HETEROCYCLIC MCHR1 ANTAGONISTS

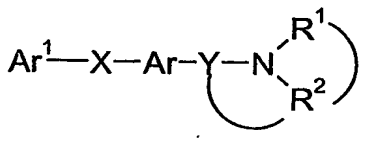
This invention relates to novel heterocycles which are antagonists at the melanin-concentrating hormone receptor 1 (MCHR1), also referred to as 11CBy, to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy.

BACKGROUND OF THE INVENTION

Obesity is a medical condition that is reaching epidemic proportions among humans in a number of countries throughout the world. It is a condition that is also associated with or induces other diseases or conditions that disrupt life activities and lifestyles. Obesity is recognized as a serious risk factor for other diseases and conditions such as diabetes, hypertension, and arteriosclerosis. It is also known that increased body weight due to obesity can place a burden on joints, such as knee joints, causing arthritis, pain, and stiffness.

Because overeating and obesity have become such a problem in the general population, many individuals are now interested in losing weight, reducing weight, and/or maintaining a healthy body weight and desirable lifestyle.

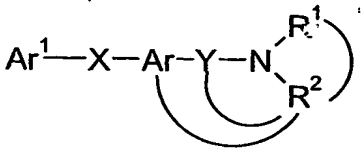
WO01/21577 (Takeda) relates to a compound of the formula



wherein Ar^1 is a cyclic group which may have substituents, X is a spacer having a main chain of 1 to 6 atoms, Y is a bond or a spacer having a main chain of 1 to 6 atoms, Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R^1 and R^2 are independently hydrogen or a hydrocarbon group which may have substituents; R^1 and R^2 together with the adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2 together with the

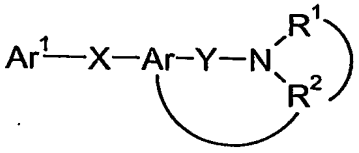
adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; or a salt thereof; and which compounds are antagonists of a melanin-concentrating hormone. Such compounds are suggested as being useful for preventing or treating obesity.

WO 01/82925A1 (Takeda) relates to a compound of the formula



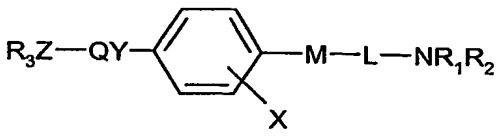
wherein Ar^1 is an optionally substituted cyclic group;
X and Y are the same or different spacers having from 1 to 6 atoms in the main chain;
Ar is an optionally substituted fused polycyclic aromatic ring;
R^1 and R^2 are the same or different hydrogen atoms or optionally substituted hydrocarbon groups, or R^1 and R^2 together with the adjacent nitrogen atoms may form an optionally substituted nitrogenous heterocycle, R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogenous heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogenous heterocycle or salts thereof.

WO 01/21577A2 (Takeda) relates to aromatic compounds of the formula



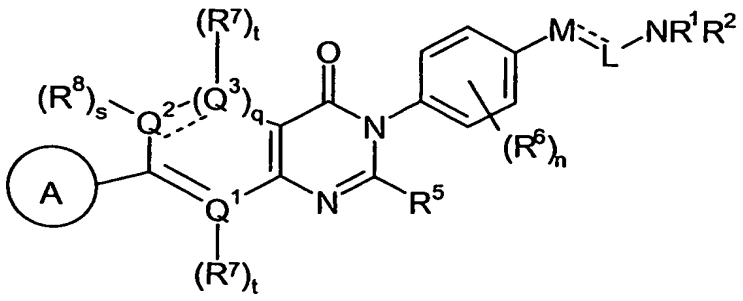
or a salt thereof, which is useful as an agent for preventing or treating obesity.

P32897WO1 (GlaxoSmithKline) relates to compounds of the formula



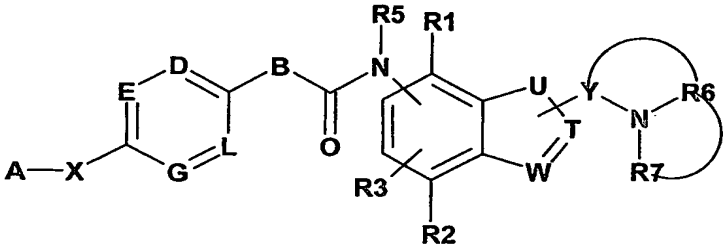
or a salt thereof , wherein M is a group selected from O, S, CO, NH or CH_2, L is a 2 or 3 membered alkylene chain, and the chain -M-L may be optionally substituted by one or more groups selected from methyl, ethyl, hydroxy or alkoxy and or which chain may contain a -C=C- double bond; R_1 and R_2 each independently represent hydrogen, C_{1-6} straight or branched alkyl which may be optionally substituted by phenyl, or C_{3-6} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups; or R_1 and R_2 together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring or a 7-10 membered bridged heterocyclic ring, which rings may be optionally substituted by a phenyl group or up to 4 C_{1-3} alkyl groups; or R_1 or R_2 may be linked to the group L or be linked as part of the substituted X on the phenyl ring to form a cyclic group; the group X may be linked to the group L to form a cyclic group which may contain an additional oxygen, a sulphur or nitrogen atom, alternatively or additionally there may be one or more substituents X selected from hydroxy, C_{1-2} alkyl, C_{1-2} alkoxy, halogen, C_{2-3} alkenyl, benzyl, CR_aNOR_b wherein R_a and R_b are independently hydrogen or methyl, methoxymethyl, methoxymethoxy or methoxyethoxy; QY is a bicyclic fused heterocyclic ring wherein Y is one ring of a bicyclic fused heterocyclic group and which is linked via nitrogen atom therein to the phenyl ring, and substituted on the second ring Q by the group ZR_3; Z is a bond or a group selected from NH, NCH_3 O, S or CH_2; R_3 is a group selected from aryl, 2-alkenyl, cycloalkyl or 2-cycloalkenyl and which R_3 group may be optionally substituted by one or more C_{1-3} alkyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-3} alkoxy, cyano, trifluoromethyl or methylthio groups, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

P32897WO2 (GlaxoSmithKline) relates to a compound of the formula comprising:



a pharmaceutically acceptable salt or solvate thereof, formulations, processes of preparing, and methods of administering to mammals are provided.

Aventis WO 03/015769A1 relates to aminoalkyl-substituted aromatic compounds of the formula below, their physiologically funcitonal derivatives and salts, as well as a method for a the production thereof. Said compounds can be suitably used as anorectic drugs.

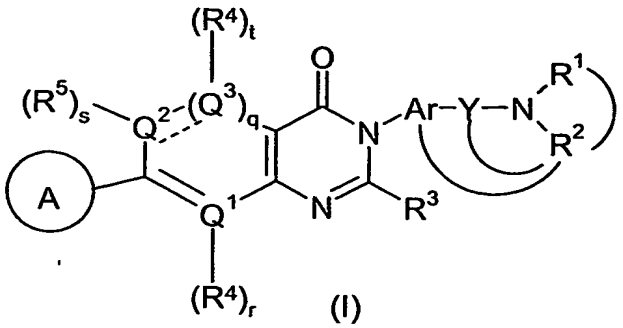


In particular, it is known that melanin-concentrating hormone ("MCH") originates in the hypothalamus and has orexigenic action (see Nature, Vol. 396, p. 670, (1998), for example). There is an on-going need for the development of a melanin-concentrating hormone antagonist useful in the treatment of obesity and other associated or related diseases and conditions.

Accordingly, we have now found a novel group of heterocycles that exhibit a useful profile of activity as antagonists of the melanin-concentrating hormone receptor (MCHR1) disclosed in Nature, Vol. 400, p. 261-265 (1999).

SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I) comprising:



(I)

a pharmaceutically acceptable salt, solvate, or phyisiologically functional derivative thereof, wherein:

(A) is aryl or heteroaryl, optionally substituted one to four times by a least one substiutent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, nitro, and alkylthio groups;

the dashed line connecting Q^2 to Q^3 represents an optional bond;

q, r, s, and t are each independently 0 or 1;

when q is 1, the bond between Q^2 and Q^3 is a double bond;

Q^1 and Q^3 are each independently C or N;

when q is 0 then Q^2 is N, S, or O;

when q is 1, then Q^2 is C or N; when q is 1 and Q^2 is N, then s is 0;

when Q^2 is S or O, s is 0;

when Q^1 is N, r is 0;

when Q^3 is N, t is 0;

R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkylthio;

when Q^1 or Q^3 is C, then each corresponding R^4 is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

when q is 1 and Q^2 is C or when q is 0 and Q^2 is N, then R^5 is selected from hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

Ar is a fused bicyclic ring optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups;

Y is a bond or a C_{1-6} alkylene, optionally substituted;

(i) R^1 and R^2 each independently are selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocycle wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo (i.e., =O), alkoxy and halo;

or (ii) R^1 and R^2 may be selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with a substituent selected from halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl;

or (iii) R^1 and R^2 together with the nitrogen atom to which they are bonded form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring, each of said 4-8 membered heterocyclic ring and said 7-11 membered bicyclic heterocyclic ring contain 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, and wherein either said heterocyclic ring or said bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

or (iv) R^2 together with the adjacent nitrogen atom and Y may form an optionally substitued nitrogen-containing heterocycle, or R^2 together with the adjacent nitorgen atom, Y, and Ar may form an optionally substitued nitrogen-containing heterocycle or salt thereof, and wherein said heterocycles are optionally substituted one to four times by at least one substituent selected

from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

In another aspect of the invention, there is provided a pharmaceutical composition for use in the treatment, prophylaxis or both of one or more conditions or indications set forth herein comprising a compound of formula (I), or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. There is also provided a method of treatment comprising the administration of the above-identified compound of formula (I) to a mammal such as a human, as well as, the use of said compound in the manufacture of a medicine for treating the conditions of obesity, diabetes, depression, and/or anxiety in a mammal (e.g., a human).

In a further embodiment of the invention, there are provided processes for the preparation a compound of formula (I).

Detailed Description of the Invention

As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, of physiologically functional derivative (such as, e.g. a prodrug), thereof.

As used herein, unless otherwise specified, the term "alkyl" and "alkylene" refer to straight or branched hydrocarbon chains containing 1 to 6 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, tert-butyl, and hexyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" also includes substituted alkyl. "Alkylene" also includes substituted alkylene. The alkyl and alkylene groups may optionally be substituted with at least one substituent selected from the group consisting of hydroxy, alkoxy, halo, amino, alkylamino, dialkylamino, thio, oxo, aryl, and cyano. Halo, alkoxy, and hydroxy are particularly preferred.

As used herein, unless otherwise specified, the term "cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless

otherwise specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may be optionally substituted with at least one substituent selected from the group consisting of hydroxy, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, and alkyl. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "alkenyl" refers to straight or branched hydrocarbon chains containing 2 to 8 carbon atoms and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl. "Alkenyl" also includes substituted alkenyl. The alkenyl group may be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, hydroxy, alkoxy, and cyano. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "cycloalkenyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example, cyclobutenyl, cyclopentenyl, and cyclohexenyl. "Cycloalkenyl" also includes substituted cycloalkenyl. The ring may be optionally substituted with at least one substituent selected from the group consisting of cyano, halo, hydroxy, $-NH_2$, $-N_3$, -CN, $-O-C_{1-3}$ alkyl, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $-C_{1-3}$ alkyl (including haloalkyl).

As used herein, the terms "halo" or "halogen" refer to fluorine, chlorine, bromine, and iodine. Preferred among these are chlorine (or "chloro") and fluorine (or "fluoro").

Unless otherwise specified, the term, "aryl" (as well as "aromatic") refers to monocyclic carbocyclic groups and fused bicyclic carbocylic groups having from 6 to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include, but are not limited to, phenyl and naphthyl. "Aryl" also includes substituted aryl, especially substituted phenyl. An aryl ring may be optionally substituted with at least one substituent selected from the group consisting of halo, alkyl (including haloalkyl), alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy, hydroxyalkyl, aminoalkyl,

carboxy, carboxamide, sulfonamide, heteroaryl (abbreviated as "Het"), amidine, cyano, nitro, and azido. Preferred aryl groups according to the invention include, but are not limited to, phenyl and substituted phenyl. Preferred substituted phenyl is a phenyl containing one or more halo groups, particularly chloro and fluoro groups.

The terms "heterocycle" and "heterocyclic" refer to a ring system composed of C and at least one other atom selected from the group consisting of N, O, and S. Heterocycles may or may not be heteroaromatic as defined below. In other words, heteroaromatics are heterocycles, but all heterocycles are not heteroaromatic.

The term "heteroaryl" and "heteroaromatic" refer to a monocyclic or bicylic aromatic ring system composed of C and at least one other atom selected from the group consisting of N, O, and S.

The terms "members" (and variants thereof, e.g., "membered") in the context of heterocyclic, heteroaryl, and aryl groups refers to the total atoms, carbon and heteroatoms (N, O, and/or S) which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine, an example of a 6-membered heteroaryl ring is pyridine, and an example of a 6-membered aryl ring is benzene.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and events that do not occur.

Formula (I) of the invention is set forth in detail as follows.


is aryl or heteroaryl, optionally substituted one to four times with at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, nitro, and alkylthio groups. Preferred among these substituted groups are halo, C_{1-3} alkyl, and C_{1-3} alkoxy. Most preferred are fluoro, chloro, and methoxy. In a preferred embodiment said  is substituted with a halo group, q is 0, Q^1 is carbon, Q^2 is sulfur, and R^4 is

hydrogen or halo. For example,  is 4-chlorophenyl and R^3 and R^4 are each hydrogen.

In the formula, the dashed line connecting Q^2 to Q^3 represents an optional bond such that the bond between Q^2 and Q^3 are connected by a double bond; and q, r, s, and t are each independently 0 or 1.

In formula (I), q is 0 or 1. When q is 1 the bond between Q^2 and Q^3 in formula (I) is a double bond. When q is 0 there is no Q^3 group. When q is 0 then Q^2 is N, S, or O. And when q is 1, Q^2 is C or N. When q is 1 and Q^2 is N, then s is 0 and there is no R^5 substituent.

Q^1 and Q^3 are each independently carbon (C) or nitrogen (N). In one embodiment, Q^1, Q^2, and Q^3 are each carbon and q, r, s, and t are 1. In another embodiment, Q^1 is carbon, Q^2 is sulfur, q and s are 0, and r is 1.

In the formula, r and t are each independently 0 or 1. When r and t are each independently 0, then there is no R^4 substituent. When r and t are each independently 1, Q^1 and Q^3 are each independently bonded by the group R^4. Each R^4 is the same or different and is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamio, hydroxy, cyano, alkylthio, and halo.

In formula (I), s is 0 or 1. When Q^2 is S or O, then s is 0 and there is no R^5 group. When Q^2 is C, then s is 1 and R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. When Q^2 is C, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In formula (I), R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Preferably, R^3 is hydrogen or a C_{1-3} alkyl; most preferably R^3 is hydrogen or methyl.

When either or both Q^1 and Q^3 are C, then R^4 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. Preferably, when either or both Q^1 and Q^3 are C, R^4 is hydrogen or C_{1-3} alkyl; most preferably R^4 is hydrogen or methyl.

When Q^2 is N, and s is 1, R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkyl amino, hydroxy, cyano, alkylthio, and halo. When Q^2 is N, and s is 1, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In the formula (I), Ar is an optionally substituted fused bicyclic ring having 9 to 14 members, optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups. That is, Ar can be a fused bicyclic ring having: (i) two aromatic rings fused together, (ii) an aromatic ring and a heteroaromatic ring fused together, (iii) two heteroaromatic rings fused together, (iv) an aromatic ring fused to a heterocyclic ring, or (v) having an aromatic ring fused to a carbocyclic ring. Preferably, Ar is selected from the group consisting of quinoline, naphthalene, benzimidazole, indole, benzothiophene, benzofuran, and benzothiazole. When Ar is a ten-membered bicyclic aromatic or ten-membered bicyclic heteroaromatic ring, then preferably Ar is quinoline or naphthalene. When Ar is a 9-membered fused bicyclic heteroaromatic ring, then preferably Ar is benzimidazole, indole, benzothiophene, benzofuran, or benzothiazole.

In the formula (I), Y is a bond or a C_{1-6} alkylene, optionally substituted as defined herein. When Ar is a ten-membered polycyclic aromatic or ten-membered polycyclic heteroaromatic ring, then preferably Y is a C_{1-3} alkylene, optionally substituted; most preferably Y is methylene ($-CH_2-$), optionally substituted. When Ar is a 9-membered fused polycyclic heteroaromatic ring, then preferably Y is a bond or a C_{1-3} alkylene, optionally substituted; most preferably Y is a bond.

In (i), R^1 and R^2 of formula (I) are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, phenyl, and 5- or 6-membered heterocycle, wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo, alkoxy, and halo.

Preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Most preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, and C_{3-6} cycloalkyl.

Or, in (ii), R^1 and R^2 are selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with at least one substituent selected from the group consisting of halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl. Preferably, when either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is a hydrogen, a C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

Additionally, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded can form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring. The 4-8 membered heterocyclic ring and/or the 7-11 membered bicyclic heterocyclic ring may contain 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. And either the heterocyclic ring or the bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, oxo, and halo. Here neither group R^1 or R^2 is linked to M or L. Preferably, R^1 and R^2 together form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicylic heterocyclic ring, having 1 or 2 heteroatoms selected from the group N, O, and S wherein said heterocyclic ring and said bicyclic heterocyclic ring may be optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

Also additionally, in (iv), R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogen-containing heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogen-containing heterocycle or salt thereof. The said nitrogen-containing heterocycles are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl,

hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, $^{t}C_{1-6}$ alkylamino, C_{1-6} dialkylamino, and halo. Preferably, R^2 together with the adjacent nitrogen atom and Y form a 3-7 membered ring when Y is a C_{1-6} alkyl group. Most preferably a 5-7 membered ring is formed. The 5-7 membered ring is optionally substituted by at least one substitutent selected from the group consisting of phenyl, one to four C_{1-3} alkyl, hydroxy, alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, or halo.

In one embodiment, when Ar is a 10-membered aromatic ring or a 10-membered heteroaromatic ring, the most preferred compounds according to this invention are selected from the group consisting of

6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-fluorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

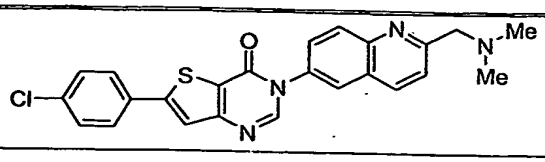
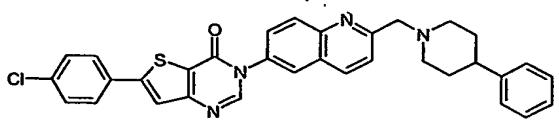
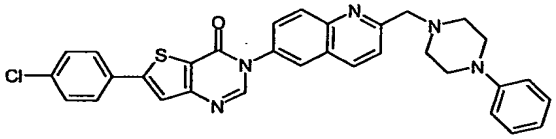
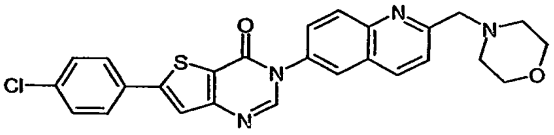
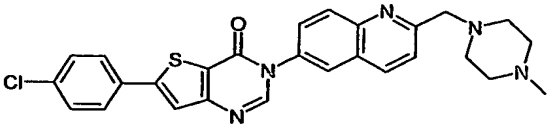
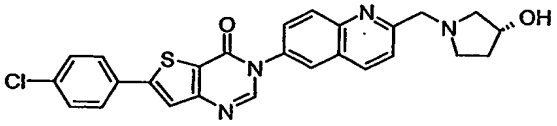
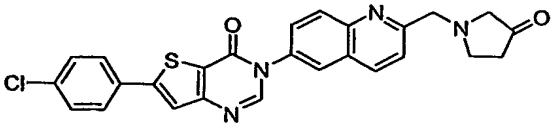
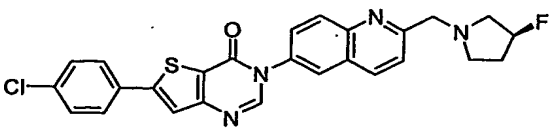
6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

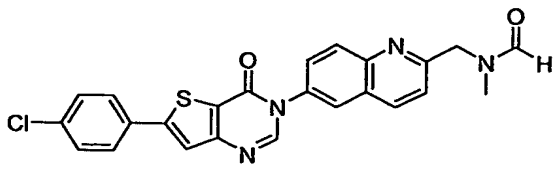
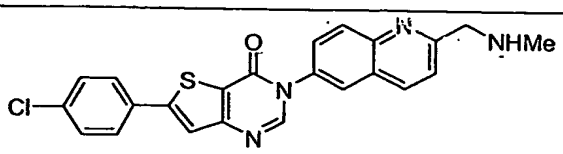
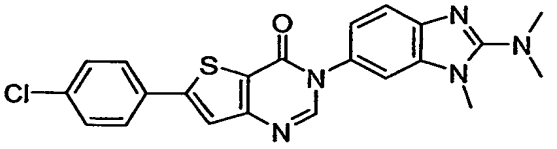
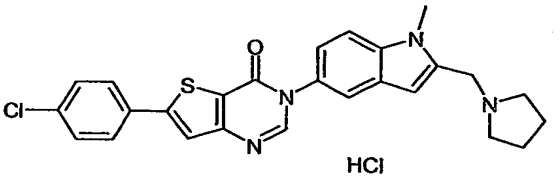
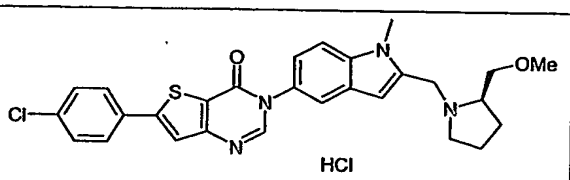
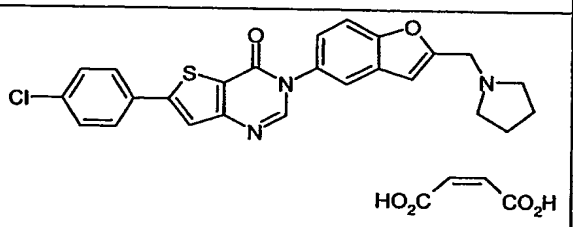
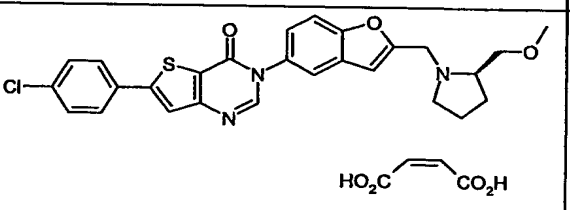
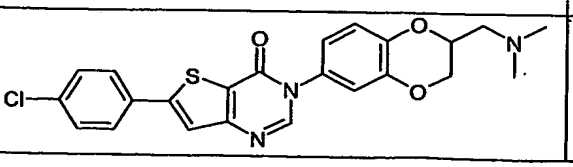
In another embodiment, when Ar is a 9-membered heteroaromatic ring, the most preferred compound according to this invention is 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

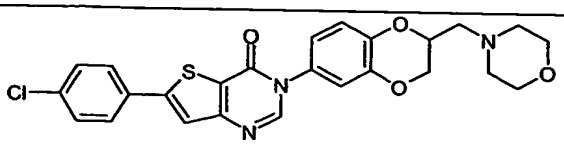
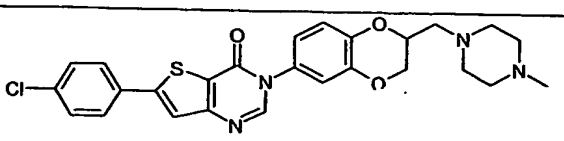
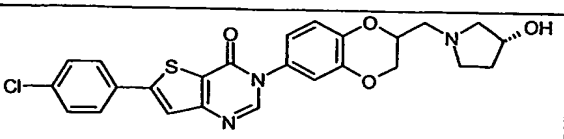
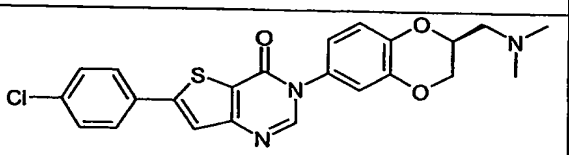
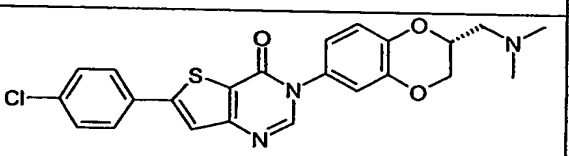
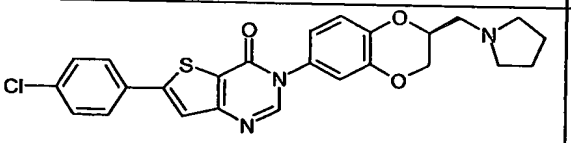
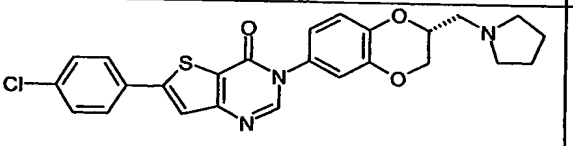
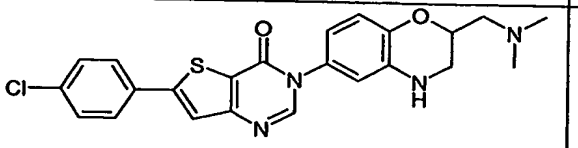
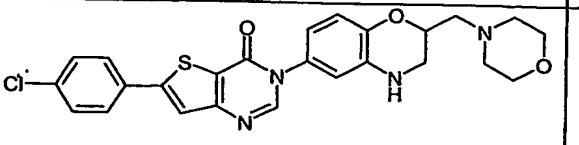
Certain compounds of formula (I) may exist in stereoisomeric forms (e.g., they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centers are inverted. Certain compounds of formula (I) may be prepared as regioisomers. The present invention covers both the mixture of regioisomers as well as individual compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

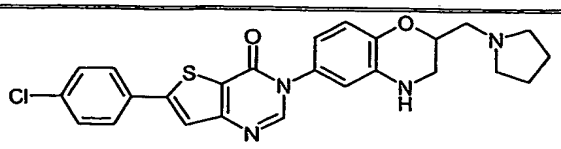
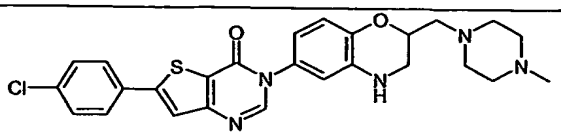
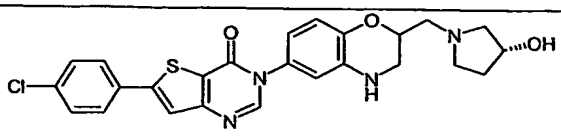
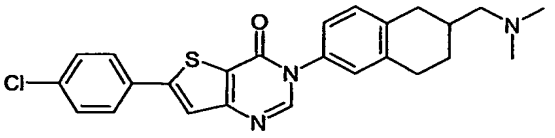
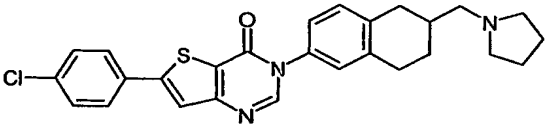
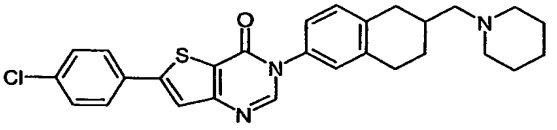
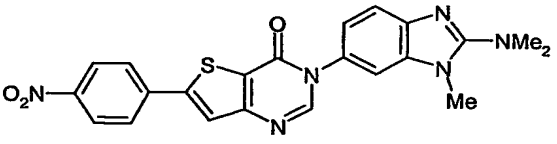
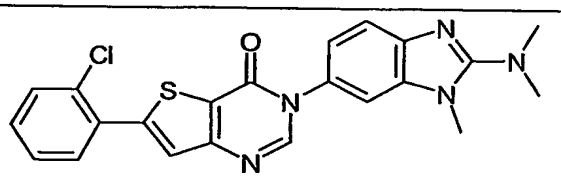
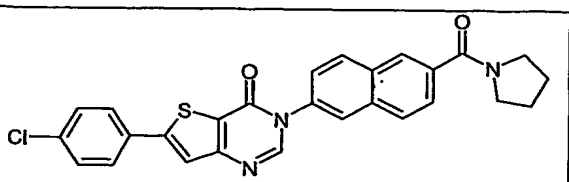
It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove. Specific compounds of formula (I) include but are not limited those set forth in Table I and/or those prepared examples herein.

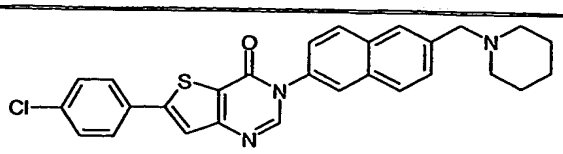
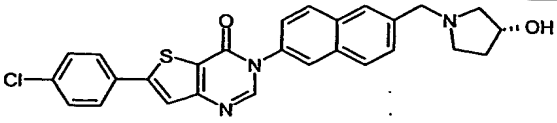
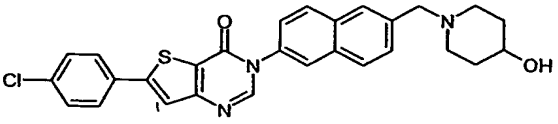
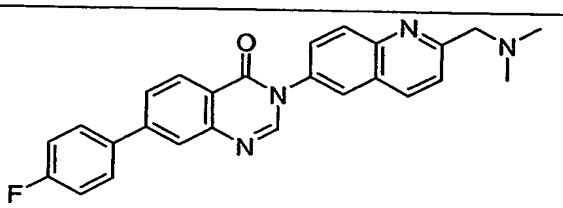
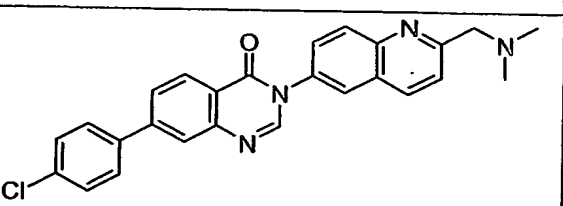
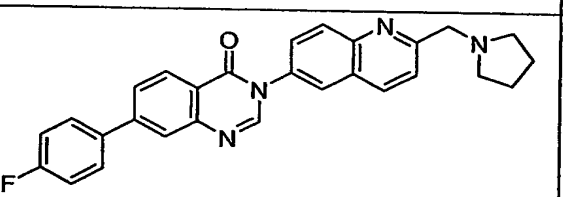
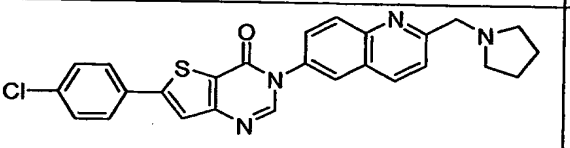
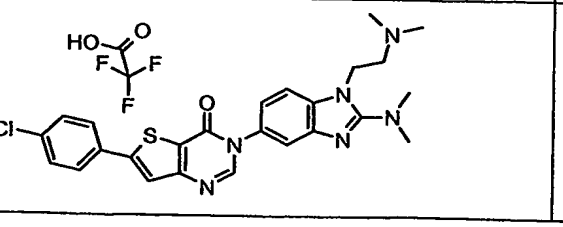
Table I

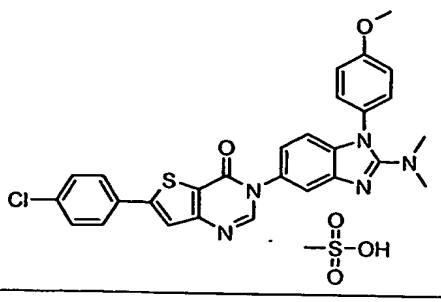
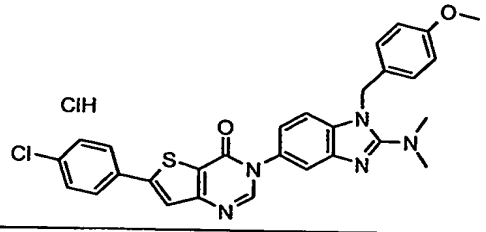
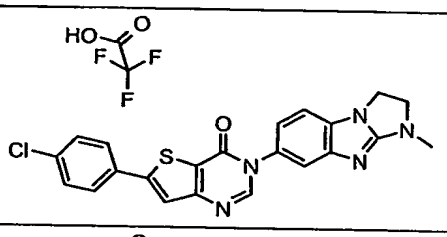
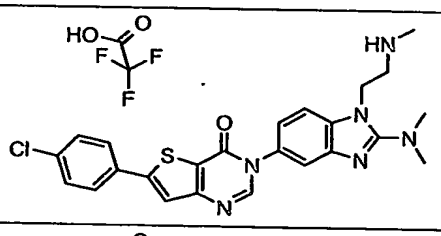
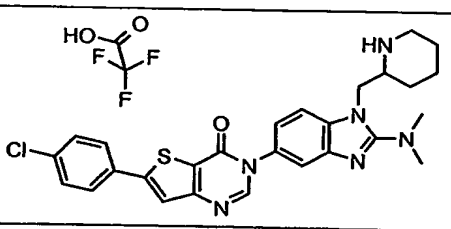
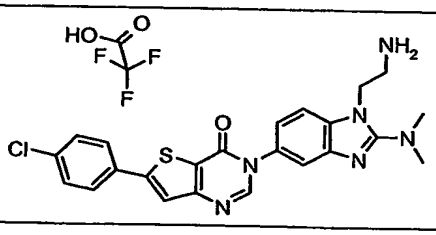
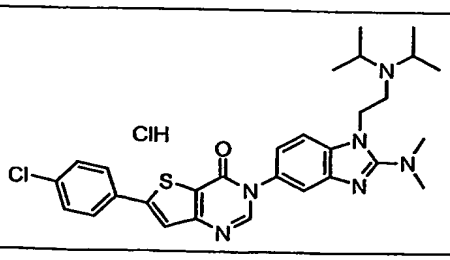
Example No.	Structure	Name
1		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
2		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
3		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
4		6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
5		6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
6		3-[2-(hydroxymethyl)-6-quinolinyl]-6(4-methylphenyl)thieno[3,2-d]pyrimidin-4(3H)one
7		6-(4-chlorophenyl)-3-{2-[(3-oxo-1-pyrrolidinyl)methyl]-6-quinolinyl}thieno[3,2-d]pyrimidin-4(3H)-one
8		6-(4-chlorophenyl)-3-(2-{[(3S)-3-fluoropyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-d]pyrimidin-4(3H)-one

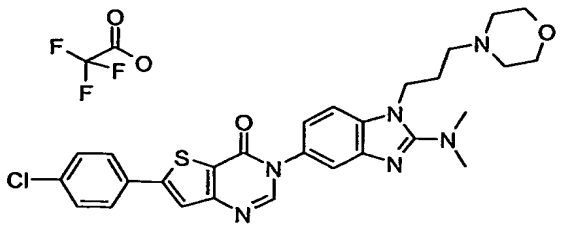
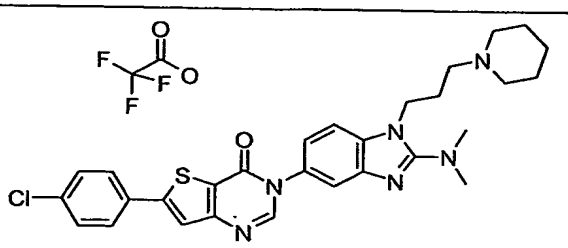
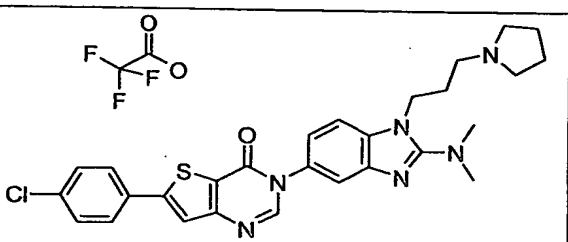
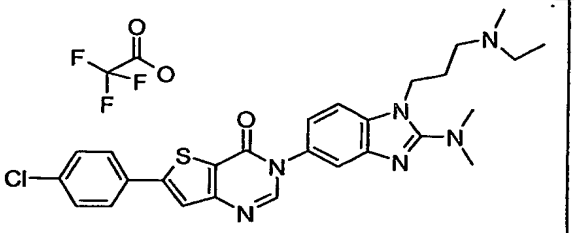
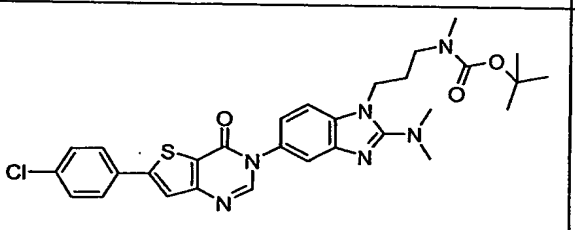
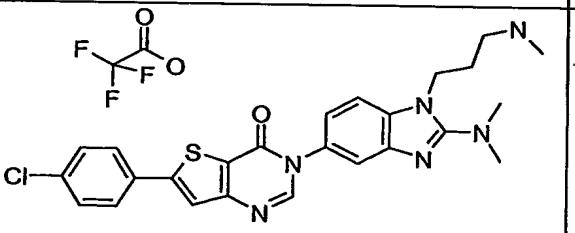
Example No.	Structure	Name
9		[6-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-quinolinyl]methyl(methyl)-formamide
10		6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
11		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
12		6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1H-indol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
13		6-(4-chlorophenyl)-3-(2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-1-methyl-1H-indol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
14		6-(4-methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
15		3-(2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-1-benzofuran-5-yl)-6-(4-methylphenyl)thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
16		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-

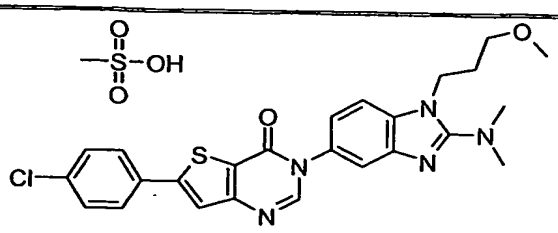
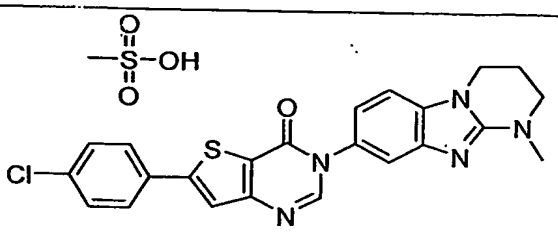
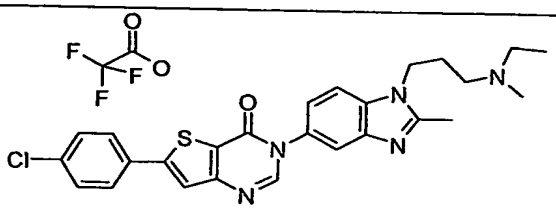
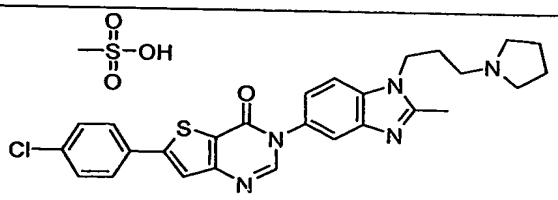
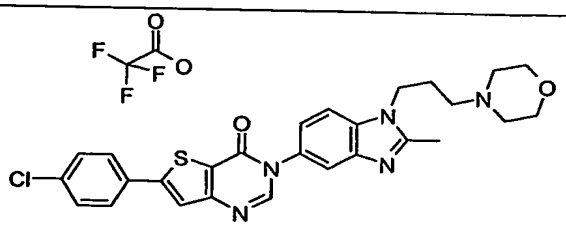
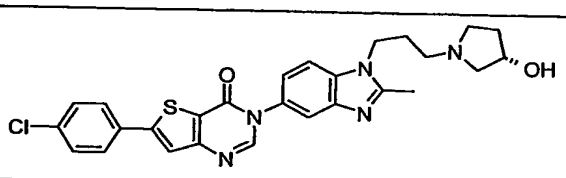
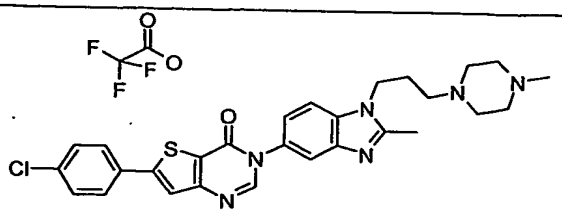
Example No.	Structure	Name
		one
17		6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
18		6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
19		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
20		6-(4-chlorophenyl)-3-{(2S)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
21		6-(4-chlorophenyl)-3-{(2R)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
22		6-(4-chlorophenyl)-3-[(2S)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
23		6-(4-chlorophenyl)-3-[(2R)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
24		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
25		6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

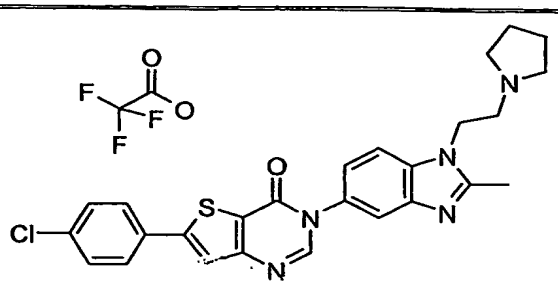
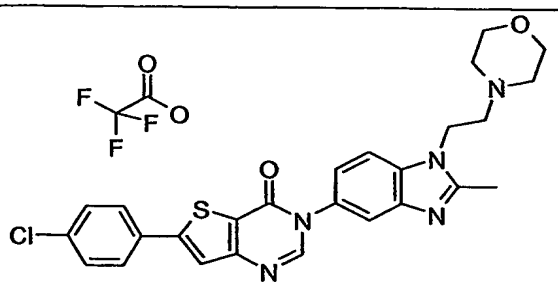
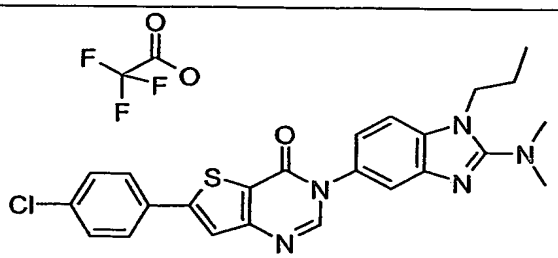
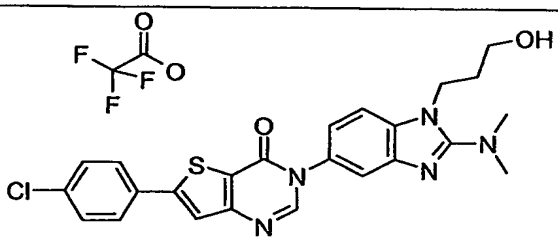
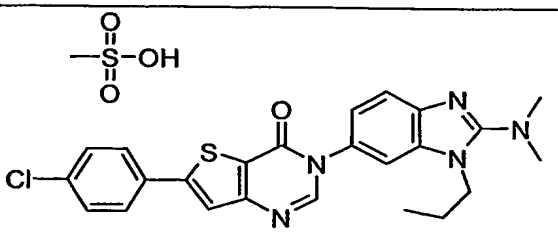
Example No.	Structure	Name
26		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
27		6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
28		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-3,4-dihydro-2H-1,4-benzoxazin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
29		6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
30		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
31		6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
32		3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]-6-(4-nitrophenyl)thieno[3,2-d]pyrimidin-4(3H)-one
33		6-(2-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
34		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylcarbonyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one

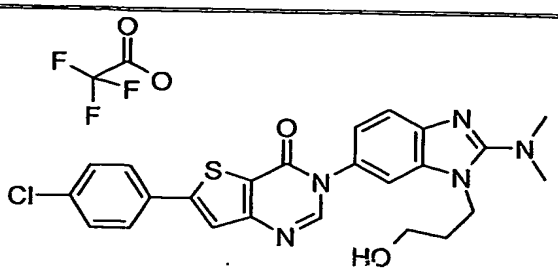
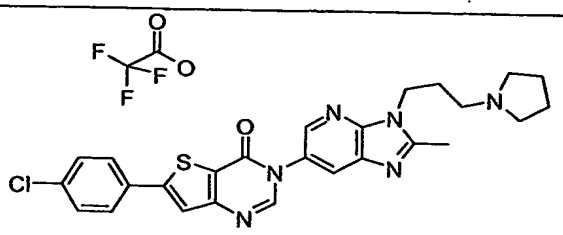
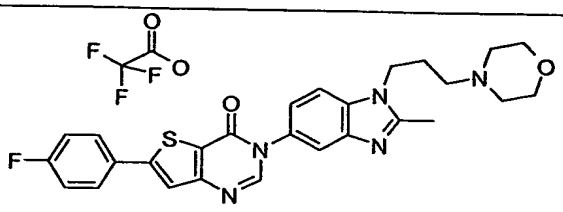
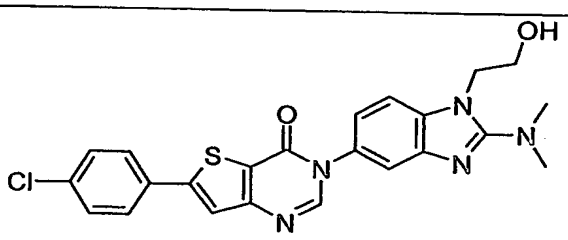
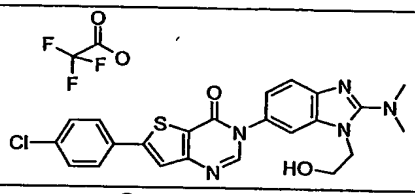
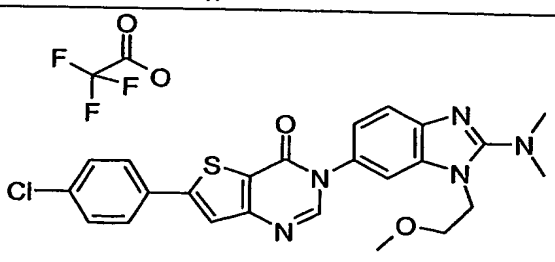
Example No.	Structure	Name
35		6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
36		6-(4-chlorophenyl)-3-(6-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-2-naphthalenyl)thieno[3,2-d]pyrimidin-4(3H)-one
37		6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
38		3-{2-[(dimethylamino)methyl]-6-quinolinyl}-7-(4-fluorophenyl)-4(3H)-quinazolinone
39		7-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-6-quinolinyl}-4(3H)-quinazolinone
40		7-(4-fluorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]-4(3H)-quinazolinone
41		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]thieno[3,2-d]pyrimidin-4(3H)-one
42		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

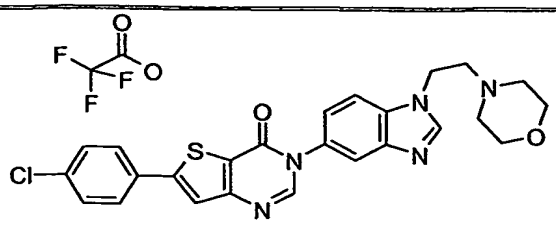
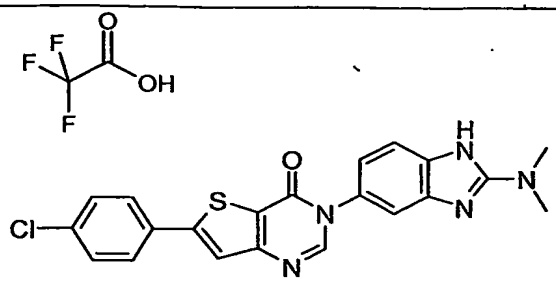
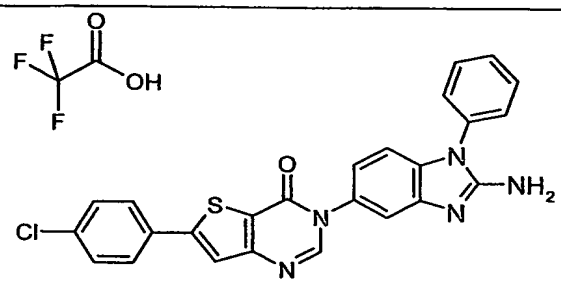
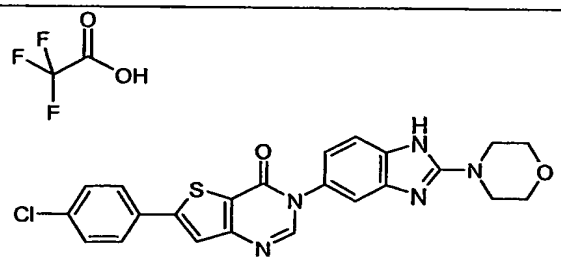
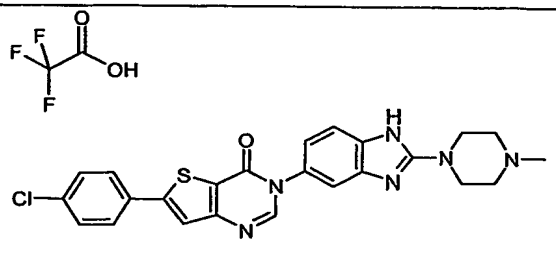
Example No.	Structure	Name
43		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[4-(methyloxy)phenyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
44		6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{[4-(methyloxy)phenyl]methyl}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
45		6-(4-chlorophenyl)-3-(1-methyl-2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-7-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
46		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methylamino)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
47		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-piperidinylmethyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
48		3-[1-(2-aminoethyl)-2-(dimethylamino)-1H-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
49		3-[1-{2-[bis(1-methylethyl)amino]ethyl}-2-(dimethylamino)-1H-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride

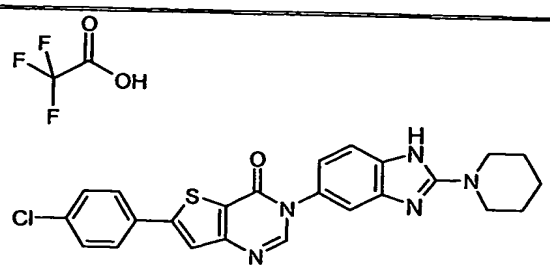
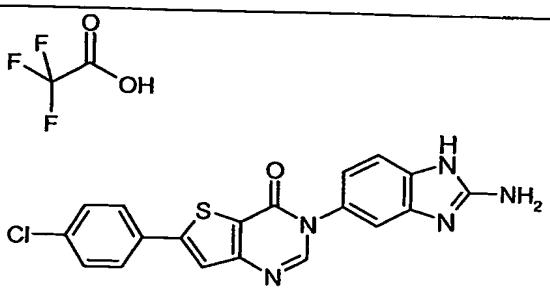
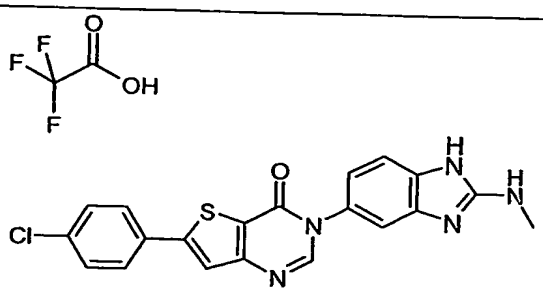
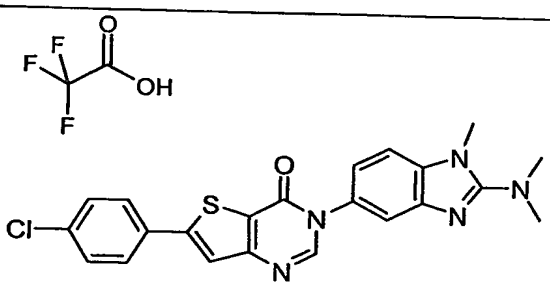
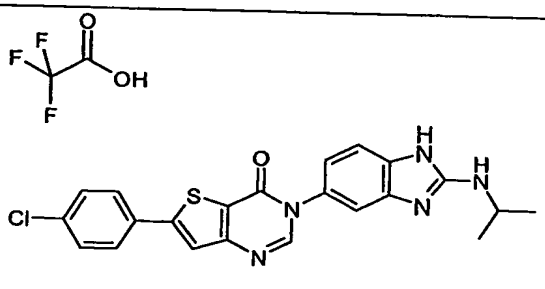
Example No.	Structure	Name
50		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-morpholin-4-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
51		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-piperidin-1-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
52		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-pyrrolidin-1-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
53		6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{3-[ethyl(methyl)amino]propyl}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
54		tert-butyl {3-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl]-2-(dimethylamino)-1H-benzimidazol-1-yl]propyl}methylcarbamate
55		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[3-(methylamino)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

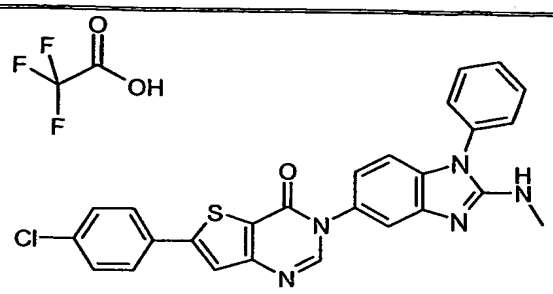
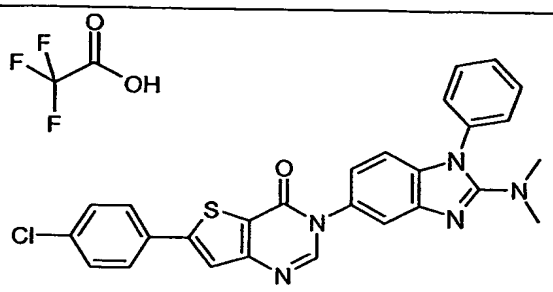
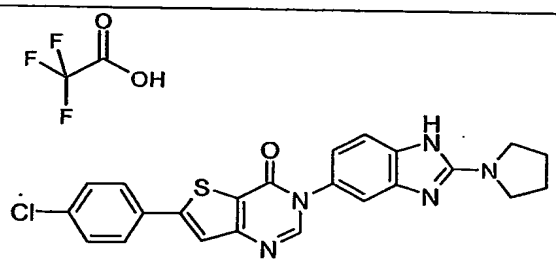
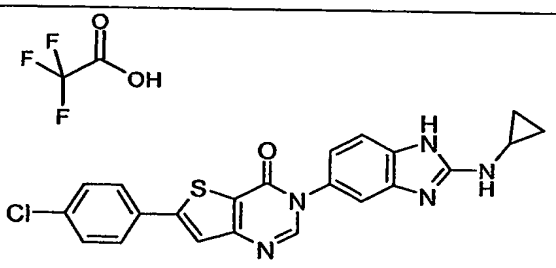
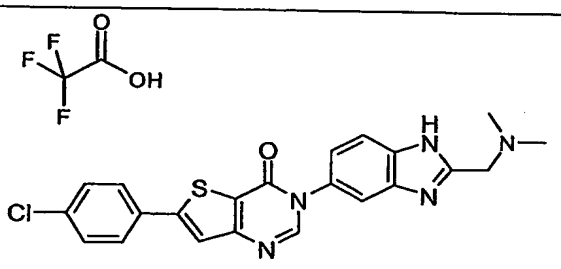
Example No.	Structure	Name
56		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-methoxypropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
57		6-(4-chlorophenyl)-3-(1-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazol-8-yl)thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
58		6-(4-chlorophenyl)-3-(1-{3-[ethyl(methyl)amino]propyl}-2-methyl-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
59		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(1-pyrrolidinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
60		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
61		6-(4-chlorophenyl)-3-(1-{3-[(3S)-3-hydroxy-1-pyrrolidinyl]propyl}-2-methyl-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one
62		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

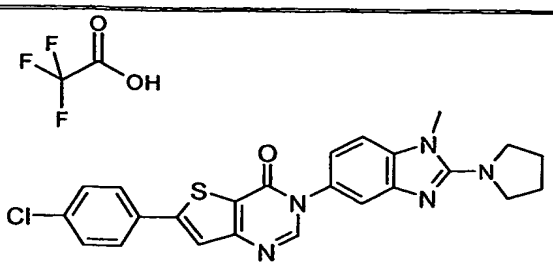
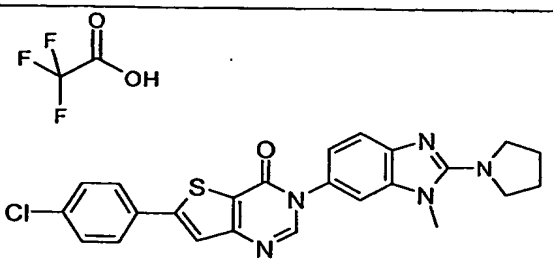
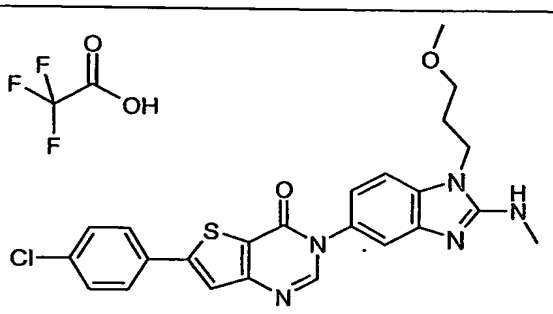
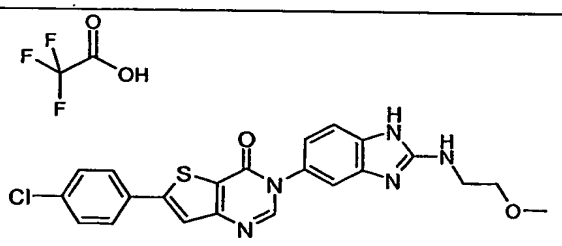
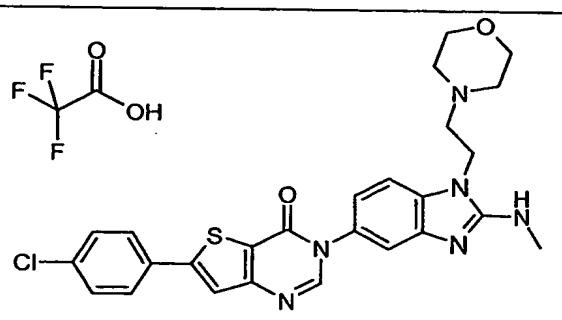
Example No.	Structure	Name
63		methyl-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
64		6-(4-chlorophenyl)-3-{2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
65		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
66		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
67		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate

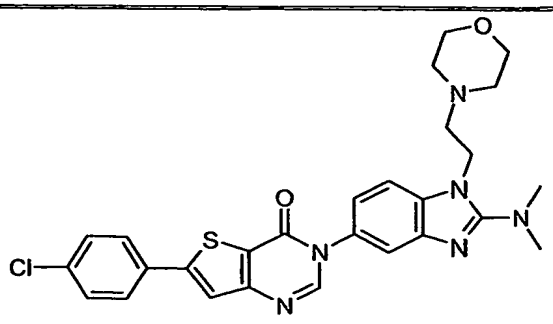
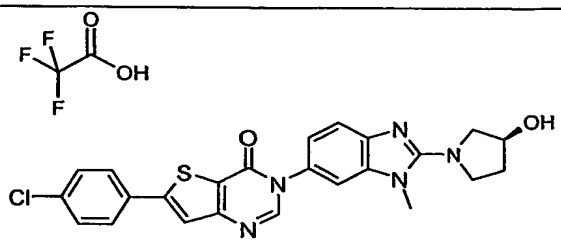
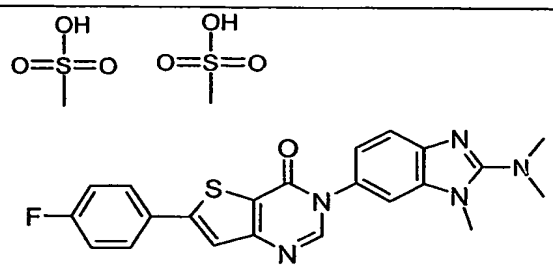
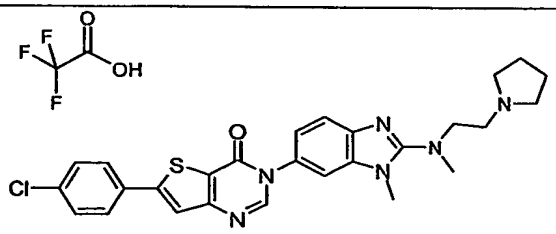
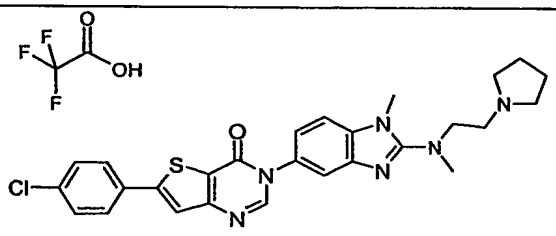
Example No.	Structure	Name
68		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
69		6-(4-chlorophenyl)-3-{2-methyl-3-[3-(1-pyrrolidinyl)propyl]-3H-imidazo[4,5-b]pyridin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
70		6-(4-fluorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
71		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
72		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
73		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methyloxy)ethyl]-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

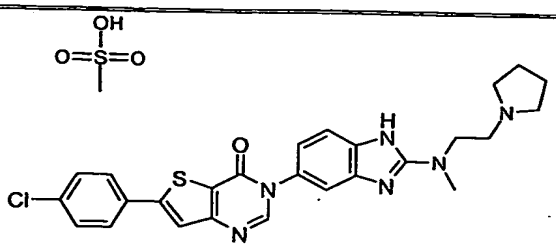
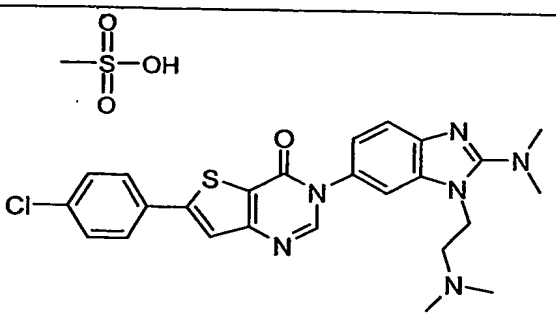
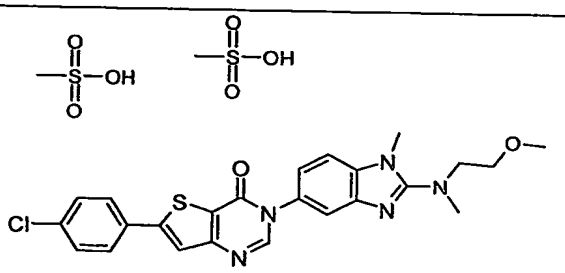
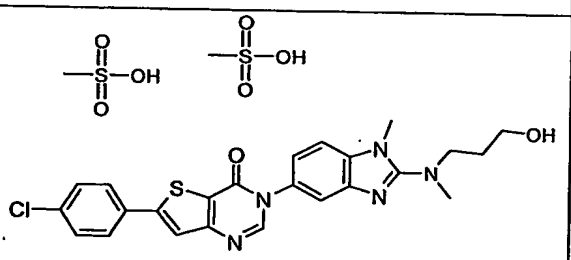
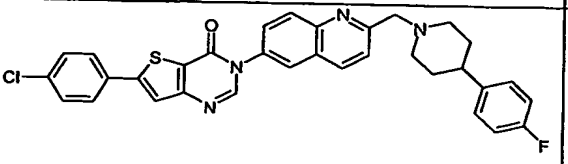
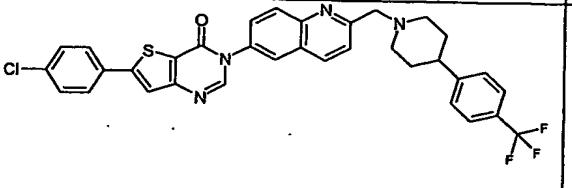
Example No.	Structure	Name
74		6-(4-chlorophenyl)-3-{1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
75		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
76		3-(2-amino-1-phenyl-1H-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
77		6-(4-chlorophenyl)-3-[2-(4-morpholinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
78		6-(4-chlorophenyl)-3-[2-(4-methyl-1-piperazinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

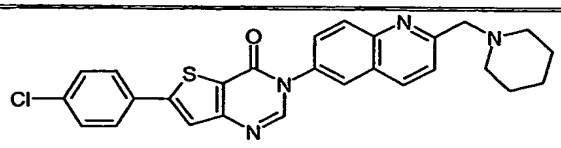
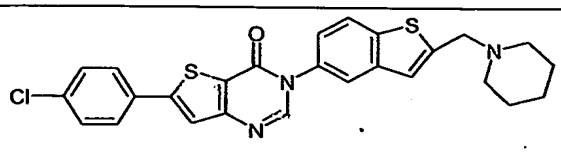
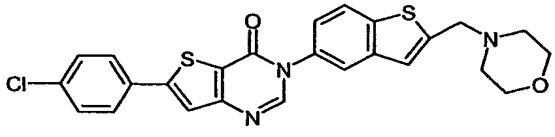
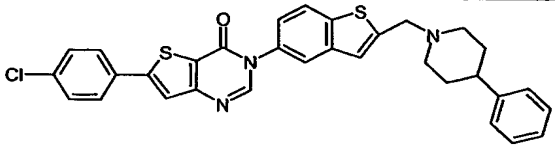
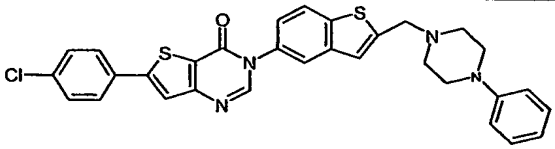
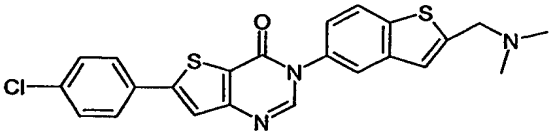
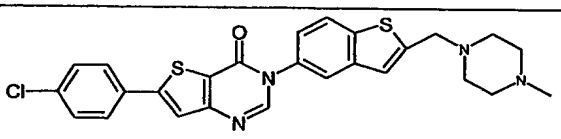
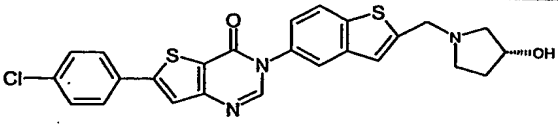
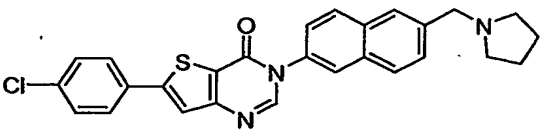
Example No.	Structure	Name
79		6-(4-chlorophenyl)-3-[2-(1-piperidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
80		3-(2-amino-1H-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
81		6-(4-chlorophenyl)-3-[2-(methylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
82		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
83		6-(4-chlorophenyl)-3-{2-[(1-methylethyl)amino]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

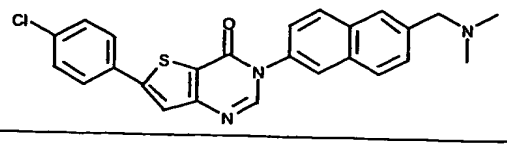
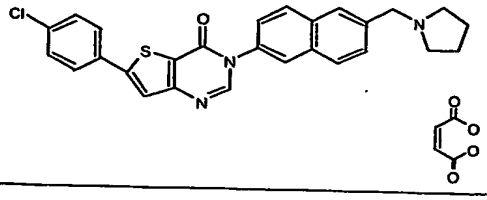
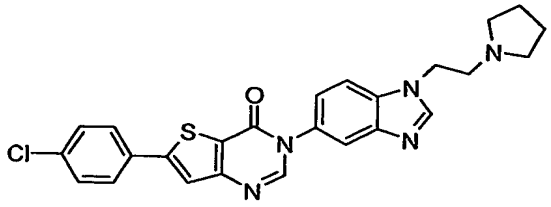
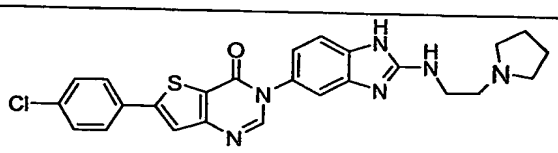
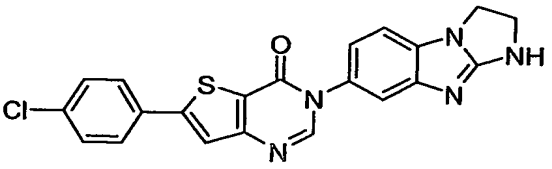
Example No.	Structure	Name
84		6-(4-chlorophenyl)-3-[2-(methylamino)-1-phenyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
85		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-phenyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
86		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
87		6-(4-chlorophenyl)-3-[2-(cyclopropylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
88		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
89		6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
90		6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
91		6-(4-chlorophenyl)-3-{2-(methylamino)-1-[3-(methyloxy)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
92		6-(4-chlorophenyl)-3-(2-{[2-(methyloxy)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
93		6-(4-chlorophenyl)-3-{2-(methylamino)-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
94		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
95		6-(4-chlorophenyl)-3-{2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-methyl-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
96		3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]-6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
97		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
98		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
99		6-(4-chlorophenyl)-3-(2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
100		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
101		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(methyloxy)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
102		6-(4-chlorophenyl)-3-{2-[(3-hydroxypropyl)(methyl)amino]-1-methyl-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
103		6-(4-chlorophenyl)-3-(2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
104		6-(4-chlorophenyl)-3-[2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

Example No.	Structure	Name
105		6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
106		6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)-1-benzothien-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
107		6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)-1-benzothien-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
108		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
109		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
110		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
111		6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
112		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxypyrrolidin-1-yl]methyl}-1-benzothien-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one
113		6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-d]pyrimidin-4(3H)-one

Example No.	Structure	Name
114		6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
115		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
116		6-(4-chlorophenyl)-3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one
117		6-(4-chlorophenyl)-3-(2-{[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one
118		6-(4-chlorophenyl)-3-(2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate or physiologically functional derivative thereof (e.g., a prodrug). The pharmaceutically acceptable salts of the compounds of

formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include maleic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, aleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic (mesylate), naphthaliene-2-sulfonic, benzenesulfonic, hydroxynaphthoic, hydroiodic, malic, steroic, tannic, and the like.

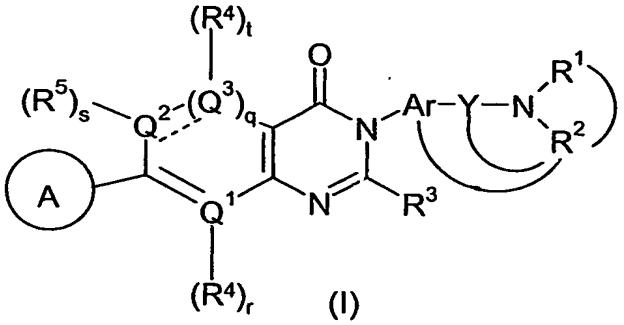
Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminum, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, and acetic acid.

The term "physiologically functional derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, a ester or an amide of a compound of formula (I), which upon administration to an animal, particularly a mammal, such as a human, is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. See, for example, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol. 1: Principles and Practice.

Processes for preparing pharmaceutically salts, solvates, and physiologically functional derivatives of the compounds of formula (I) are conventional in the art. See, e.g., Burger's Medicinal Chemistry and Drug Discovery,5th Edition, Vol.1: Principles and Practice.

Compounds of formula (I) below are conveniently prepared in accordance with the reaction schemes and/or processes outlined or described herein.

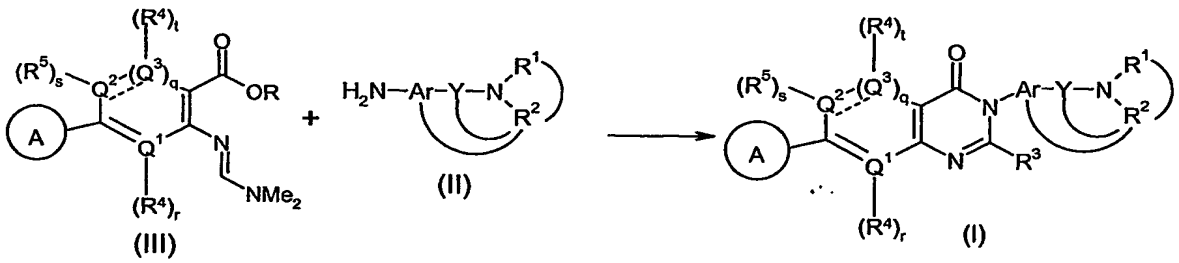


(I)

As will be apparent to those skilled in the art, in the processes described below for the preparation of compounds of formula (I), certain intermediates, may be in the form of pharmaceutically salts, solvates or physiologically functional derivatives of the compound. With respect to any intermediate employed in the process of preparing compounds of formula (I), the terms or identifiers have the same meanings as noted above with respect to compounds of formula (I). In general, processes for preparing pharmaceutically acceptable salts, solvates and physiologically functional derivatives of intermediates are known, and the process for preparing pharmaceutically acceptable salts, solvates and physiological functional derivatives of the compounds of formula (I) are similar and set forth below.

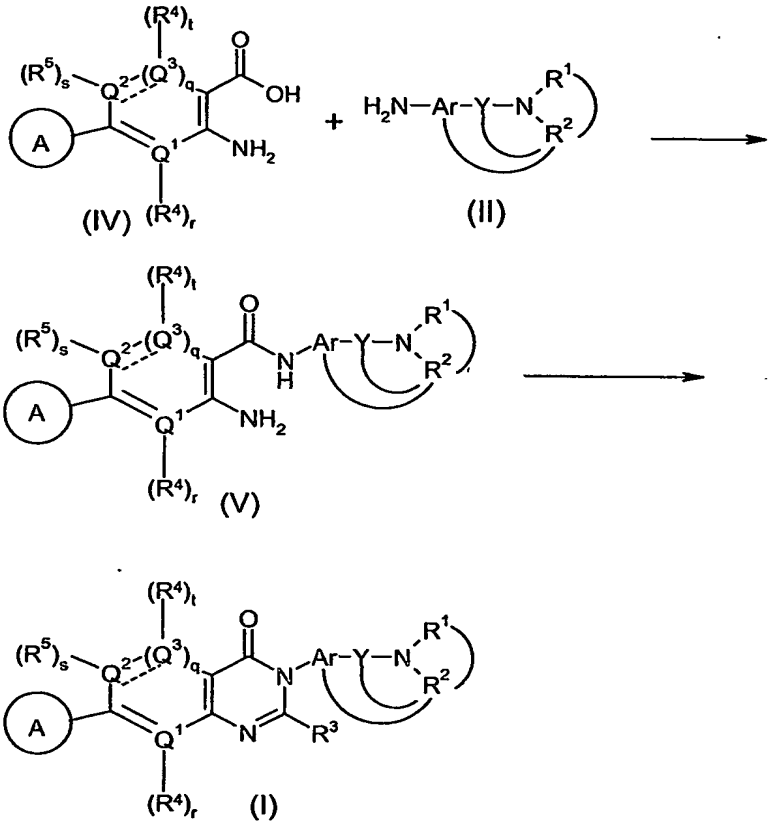
Unless otherwise stated,  , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t are as defined in formula (I) for all of the processes enumerated herein.

Thus, compounds of formula (I) wherein R^5 is H may be prepared by reaction of an aniline of formula (II) with a formamidine ester of formula (III) wherein R is C_{1-4} alkyl.

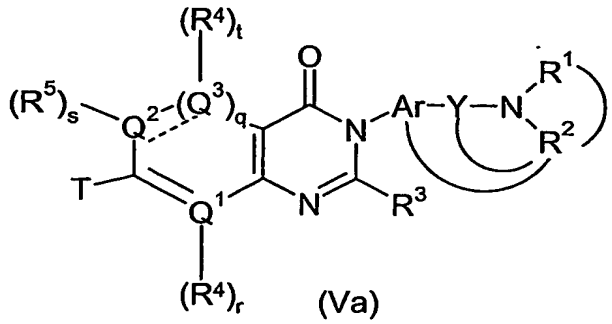


(III) (II) (I)

Compounds of formula (I) can also be prepared by an amide coupling of the corresponding amino acid (IV) and the desired aniline (II) in a solvent, such as methylene chloride, with amide coupling agents such as EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride), followed by cyclization in refluxing carboxylic acids, such as formic acid.



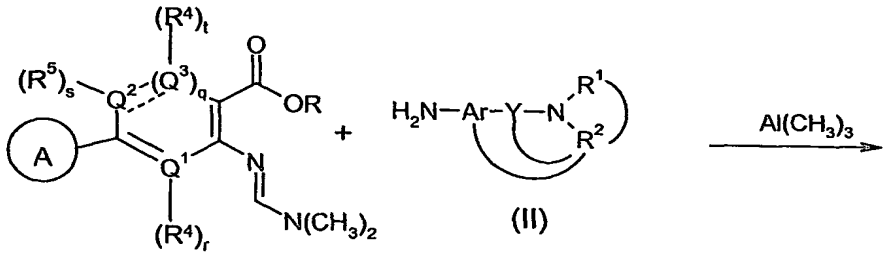
Compounds of formula (I) may also be prepared by reaction of a compound of formula (Va)



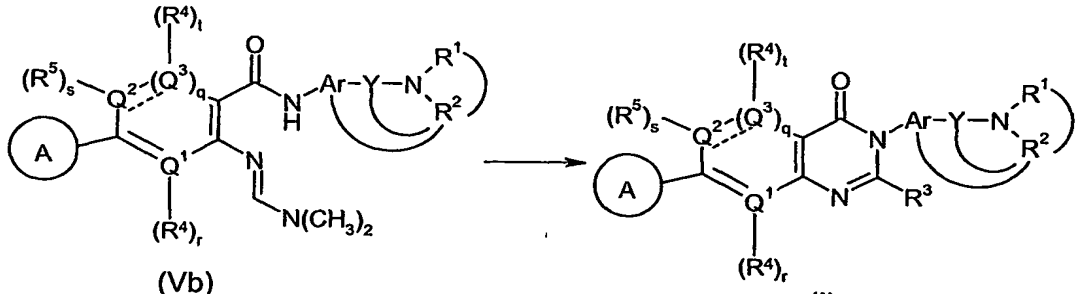
with a compound capable of introducing the group (A), and T is a leaving group (e.g., chloro, bromo, iodo, and triflate (-OSO_2CF_3)).

Thus compounds of formula (I) may be prepared from the compound of formula (Va) with a boronic acid and a palladium catalyst using a Suzuki coupling reaction or with an organostannane reagent and a palladium catalyst using a Stille coupling reaction.

Compounds of formula (I) may also be prepared by reaction of an amino ester of formula (III) wherein R is C_{1-4} alkyl with an aniline of formula (II) in a solvent such as dichloromethane or 1,2-dichloroethane in the presence of trimethylaluminum to produce a compound of formula (Vb) and cyclizing said compound of formula (Vb).

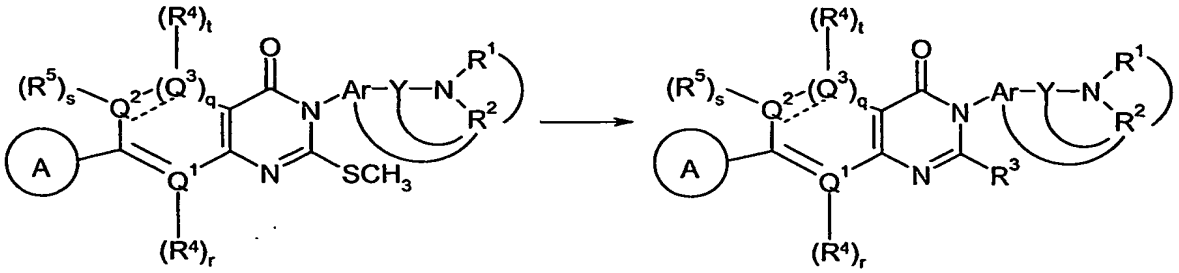


(III) (II)



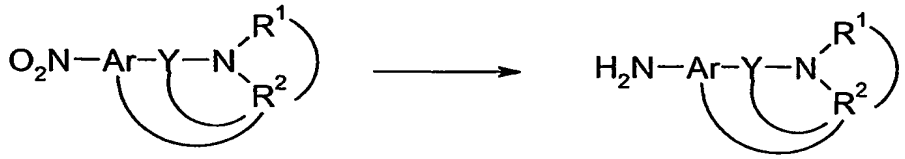
(Vb) (I)

Compounds of formula (I) wherein R^3 is hydrogen may also be prepared by reaction of a sulfur-containing compound such as (VI) with a reductant, such as Raney Nickel, in a solvent such as ethanol.



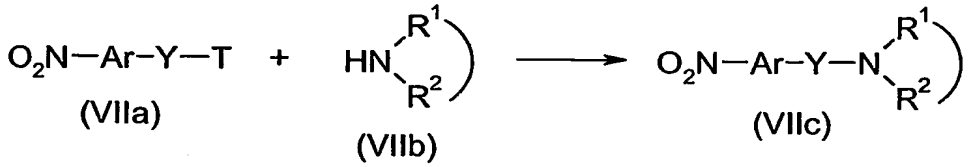
(VI) (I)

Compounds of formula (II) may be prepared by reduction of the corresponding nitroaromatic (VII) using hydrogen and a catalyst (e.g., 10% Pd on carbon), stannous chloride, or sodium dithionite.



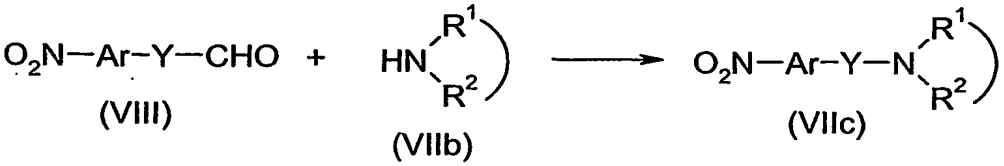
(VII) (II)

Compounds of formula VIIc wherein Y is CH_2 can be prepared from a compound (VIIa) and an amine (VIIb) and T is a leaving group (e.g., Cl, Br, I, mesylate, and tosylate).



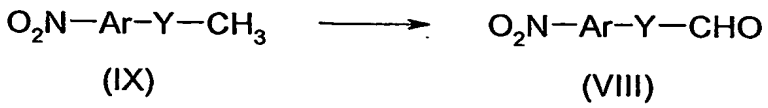
(VIIa) (VIIb) (VIIc)

Alternatively, compounds of this type can be made by reductive amination of an aldehyde of formula (VIII) by an amine of formula (VIIb) in the presence of a reducing agent such as a sodium borohydride.



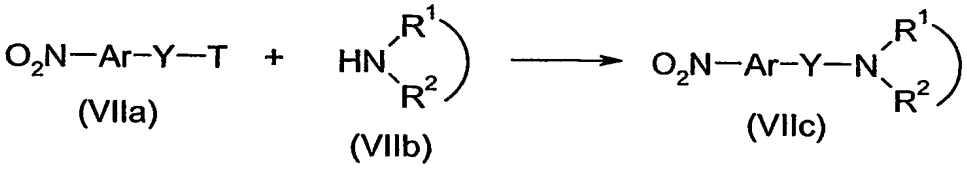
(VIII) (VIIb) (VIIc)

Compounds of formula (VIII) in which Y is a bond can be prepared by reaction of a compound of formula (IX) (in which Y is a bond) with an oxidant such as selenium dioxide in a solvent such as dioxane.



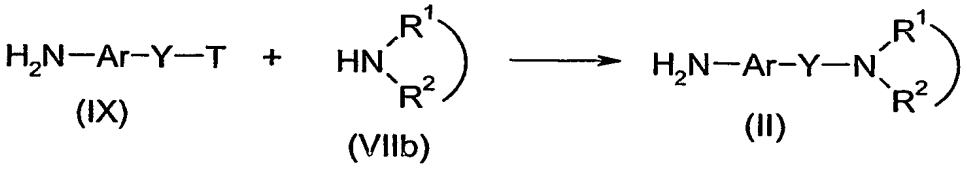
(IX) (VIII)

Compounds of formula VIIc can be prepared from a compound (VIIa) and an amine (VIIb) in which T is a leaving group.



(VIIa) (VIIb) (VIIc)

Compounds of formula (II) can be prepared from a compound (IX) and an amine (VIIb) in which T is a leaving group.



(IX) (VIIb) (II)

In the present invention, the compounds of formula (I) are believed to have a role in the treatment of depression, anxiety, obesity and/or diabetes. Compounds of the present invention are antagonists of a MCHR1 and can be used for the treatment of a disease caused by or attributable to a melanin-concentrating hormone. Compounds of the invention may reduce hunger, suppress appetite, control eating, and/or induce satiety.

The present invention provides methods for the treatment of several conditions or diseases such as obesity, diabetes, depression (eg., major depression and/or bipolar disorder), and/or anxiety. Such treatment comprises the step of administering a therapeutically effective amount of the compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. Such treatment can also comprise the step of administering a therapeutically effective amount of a

pharmaceutical composition containing a compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and preventing or delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject.

As used herein, the term "therapeutically effective amount" means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, animal (including human) that is being sought, for instance, by a researcher or clinician.

The precise therapeutically effective amount of the compounds of formula (I) will depend on a number of factors including, but not limited to, the age and weight of the subject being treated, the precise disorder requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. Typically, the compound of formula (I) will be given for treatment in the range of about 0.1 to about 200 mg/kg body weight of recipient (animal) per day and more usually in the range of about 1 to about 100 mg/kg body weight per day. In general, acceptable daily dosages, may be from about 0.1 to about 5000 mg/day, and preferably from about 0.1 to about 2000 mg/day. Unit doses will normally be administered once or more than once per day, preferably about 1 to about 4 times per day.

The administration of compounds of the invention to an animal, particularly a mammal such as a human, may be by way of oral (including sub-lingual), parenteral, nasal, rectal or transdermal administration. Preferably oral administration is employed.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of formula (I) may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation. Accordingly, the invention further provides a pharmaceutical composition comprising a compound of formula (I). The

pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s), and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I) with one or more pharmaceutically acceptable carriers, diluents, and /or excipients.

Pharmaceutical formulations may be presented in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of formula (I) or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example, by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the carrier(s), diluent(s), and/or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules (including soft gelatin capsules, hard gelatin capsules, and capsules made from other polymers such as hydroxypropylmethylcellulose) or tablets; powders or granules; solutions, emulsions, or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions. For instance, for oral administration in the form of a tablet or capsule (e.g., hard,

soft, elastic, gelatinous and/or non-gelatinous), the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, opaque, dispersing and coloring agent or dye can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin and/or non-gelatinous sheaths. Glidants and lubricants, such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, cellulosic polymers (e.g., hydrogels (HPMC, HPC, PVA), and the like), carboxymethylcellulose, polyethylene glycol, waxes, polyvinylpyrrolidone, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators (disintegrants) include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granuated by wetting with a

binder such as a syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material (e.g., HPMC) and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

The drug may be dissolved or dispersed in a volatile liquid such as water or ethanol and sprayed onto nonpareil beads. A binder such as sucrose, polyvinylpyrollidone, hydroxypropylmethylcellulose, or the like may be used. After at least one coating, protective coat(s) of a polymer such as hydroxypropylmethylcellulose may be applied and/or a sustained or delayed release coating(s) may be applied. Such coated beads may optionally be compressed into tablets or filled into capsules.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like. The compound of formula (I) can also

be incorporated into a candy, a wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicament. Oral dosage forms may be taken with or without water.

Additionally, the present invention comprises a compound of formula (I) in combination with at least one other species selected from the group consisting of at least one agent or drug for treating obesity, diabetes (e.g., rosiglitazone and/or metformin), hypertension, and arteriosclerosis. In particular, a compound of formula (I) may be combined with at least one species for the treatment of obesity selected from the group of human ciliary neurotrophic factor, a CB-1 antagonist or inverse agonist (such as rimonabant), a neurotransmitter reuptake inhibitor (such as sibutramine, bupropion, or bupropion HCl), a lipase inhibitor (such as orlistat), an MC4R agonist, a 5-HT2c agonist, and a ghrelin receptor agonist or antagonist.

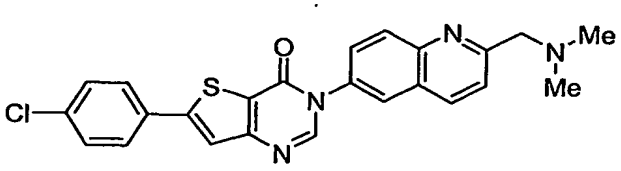
Also, the invention can be the use of a compound of formula (I) for the manufacture of a medicine (that is, medicament) for the treatment of a condition selected from the group consisting of obesity, diabetes, depression, and anxiety in a mammal.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way, the invention being defined by the claims which follow. All references cited in this specification are hereby incorporated by reference.

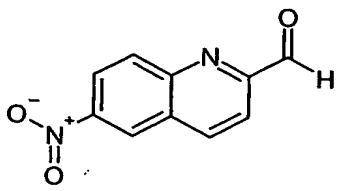
Reagents are commercially available or are prepared according to procedures in the literature.

Experimental Section

Example 1

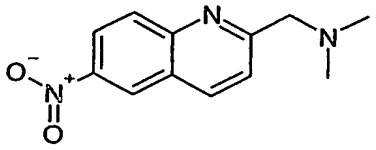


6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 6-nitroquinoline-2-carbaldehyde

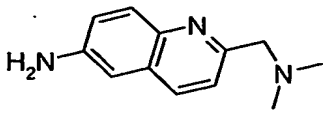
To a hot solution of selenium dioxide (41.6 g, 375 mmol) in dioxane (185 mL) and water (35 mL) was added 2-methyl-6-nitroquinoline (47.0 g, 250 mmol). The mixture was refluxed for 30 minutes. The selenium black was filtered off and the filtrate was concentrated by rotary evaporation. The resulting solid was filtered, washed with a saturated solution of sodium bicarbonate and then water, and dried to give the product as a tan solid (44.8 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.21 (d, J = 2.6 Hz, 1H), 8.97 (d, J = 8.5 Hz, 1H), 8.59 (dd, J = 2.6 Hz, J' = 9.2 Hz, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H).



Step B: *N*,*N*-dimethyl-1-(6-nitroquinolin-2-yl)methanamine

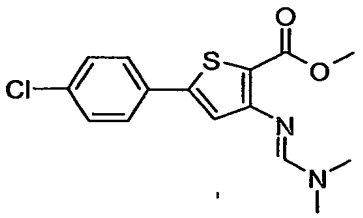
To a solution of 6-nitroquinoline-2-carbaldehyde (the intermediate produced in Example 1, Step A; 44.8 g, 221 mmol) in dichloroethane (800 mL) and methanol (320 mL) was added dimethylamine (221 mL, 442 mmol, 2 M in THF) and acetic acid (13.3 g, 221 mmol). The mixture was stirred at room temperarture for 20 min at which point sodium triacetoxyborohydride (65.6 g, 309 mmol) was added in 3 portions with vigorous mechanical stirring. The reaction mixture was stirred overnight. To the reaction mixture was added saturated sodium bicarbonate solution (300 mL) and the mixture was extracted with dichloromethane (2 x 400 mL). The organic layer was filtered through Celite. The filtrate was washed with brine (200 mL), dried and concentrated to give a tan solid (41.1 g, 80% yield). ^{1}H NMR (300 MHz,

DMSO-d_6) δ 9.05 (d, J = 2Hz), 8.67 (d, J = 9.6 Hz, 1H), 8.43 (dd, J = 2.2 Hz, J' = 12.3 Hz), 8.17 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 3.75 (s, 2H), 2.24 (2, 6H).



Step C: 2-[(dimethylamino)methyl]-6-quinolinamine

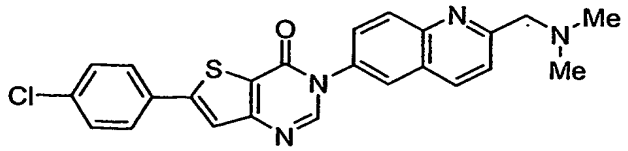
N,*N*-Dimethyl(6-nitro-2-quinolinyl)methanamine (the intermediate produced in Example 1, Step B; 365 mg, 1.58 mmol) was dissolved in EtOH. A catalytic amount of Pd/C was added. The mixture was degassed and was stirred under 1 atm H_2 for 5 h. The mix was filtered through celite and the solvents were removed to give the desired intermediate (290 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 2.30 (6H, s), 3.68 (2H, s), 6.87 (1H, m), 7.11 (1, m), 7.15 (1H, s), 7.43 (1H, d, J = 8.8 Hz), 7.86 (1H, m). LCMS m/z = 202 (m + H^+).



Step D: methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate

A mixture of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (37.3 mmol, 10.0 g) and N,N-dimethylformamide dimethyl acetal (74.7 mmol, 8.9 g) in ethanol (350 mL) was heated to reflux for 3 hours. The solvent was removed by rotary evaporation. To the residue 15 mL of toluene was added and the solvent was removed by rotary evaporation. This was repeated three times. To the resulting sticky residue, 20 mL hexanes were added followed by the gradual addition of ethyl acetate at 0°C until it solidified. The resulting solid was collected by filtration giving the desired intermediate (11.9 g, 98.9%). ^{1}H

NMR ($CDCl_3$): δ 3.08 (6H, d, J = 6.5 Hz), 3.81 (3H, s), 6.98 (1H, s), 7.35 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.69 (1H, s). LCMS m/z = 323 ($m + H^+$).

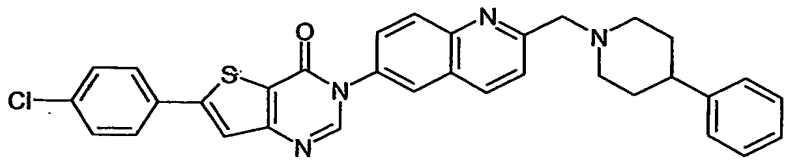


Step E: 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

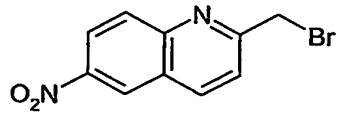
A 2 M solution of $AlMe_3$ in hexanes (0.96 mL, 1.92 mmol) was added slowly to a solution of 2-[(dimethylamino)methyl]quinolin-6-amine (the intermediate produced in Example 1, Step C; 0.34 g, 1.69 mmol) in dichloroethane (6 mL) at room temperature under N_2. After 15 min, a solution of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (the intermediate produced in Example 1, Step D; 0.50 g, 1.54 mmol) in dichloroethane (3 mL) was added and stirred at room temperature for 0.5 h. The solution was heated to reflux for 3 h then cooled to room temperature. Formic acid (6 mL) was added carefully and the mixture was heated to reflux for 4 h. Upon cooling to room temperature, an aqueous 1 N NaOH solution (50 mL) was added followed by CH_2Cl_2 (400 mL) and water (300 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a tan solid (0.79 g) with ca. 85% purity. The solid was partially dissolved in hot $CHCl_3$ (20 mL), filtered, and concentrated. The resulting solid was dissolved in $CHCl_3$ (15 mL) and then Et_2O (25 mL) was added which produced a white precipitate. The solid was filtered and dried under vacuum to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a white powder (0.33 g, 48%). The remaining impure material was subsequently purified in the same manner as described above to yield an additional 0.10 g of the title compound (63% overall yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.9 Hz, 1H), 8.25 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H),

7.91 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 2.4, 9.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 3.83 (s, 2H), 2.37 (s, 6H). EI-LCMS *m/z* 447 (M+H).

Example 2

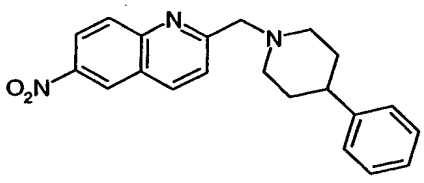


6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



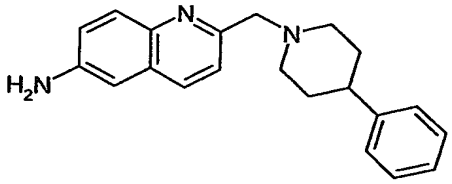
Step A: 2-(bromomethyl)-6-nitroquinoline

A solution of 2-methyl-6-nitroquinoline (3.0 g, 15.9 mmol) and N-bromosuccinimide (3.11 g, 17.49 mmol) in 36 mL chloroform in a pyrex round bottomed flask was stirred in the presence of a UV lamp at 40 °C for 2 d . After cooling, the mixture was washed with aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic layers dried over sodium sulfate. Concentration followed by column chromatography on silica gel using hexane:ethyl acetate 7:3 afforded 2-(bromomethyl)-6-nitroquinoline as pale yellow solid (2.67 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.78 (d, J = 8.6 Hz, 1H), 8.52 (d, J = 9.8 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 4.93 (s, 2H); ES-LCMS *m/z* 267 (M+H).



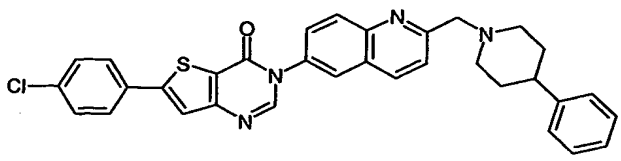
Step B: 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline

To a solution of 2-(bromomethyl)-6-nitroquinoline (the intermediate produced in Example 2, Step A; 1.0 g, 3.76 mmol) in THF at room tempreature was added Hunig's base (1.31 mL, 7.52 mmol) followed by the addition of 4-phenylpiperidine (0.61 g, 3.76 mmol). The contents were stirred for 3 h at room temperature. The crude reaction mixture was concentrated and loaded directly over a silica gel column using hexane:ethyl acetate 1:1 as the eluent to afford 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline as a brown solid (1.05 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.67 (d, J = 9.0 Hz, 1H), 8.43 (d, J = 9.4 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.29 – 7.14 (m, 5H), 3.83 (s, 2H), 2.94 (m, 2H), 2.51 (m, 2H), 2.23 (m, 2H), 1.73 – 1.67 (m, 3H); ES-LCMS *m/z* 348 (M+H).



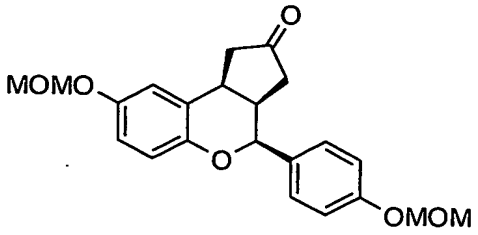
Step C: 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine

To a solution of 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline (the intermediate produced in Example 2, Step B; 1.0 g, 2.88 mmol) in 30 mL THF/EtOH (1:1) was added 0.1 g of Pd/C (10%) and the contents stirred under hydrogen gas (40 psi) for 6 h. The reaction was then filtered through celite, washed with EtOH and the contents concentrated under vacuum to afford 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine as a green solid (0.8g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.39 – 7.10 (m, 6H), 6.78 (s, 1H), 3.45 (s, 2H), 2.94 (m, 2H), 2.52 (m, 2H), 2.16 (m, 2H), 1.74 – 1.65 (m, 3H); ES-LCMS *m/z* 320 (M+H).



Preparation 18

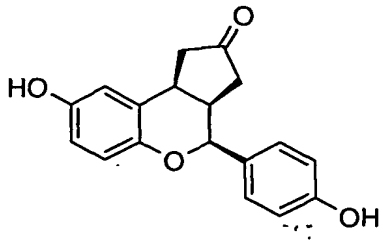
8-Methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,3a,4,9b-tetrahydro-3H-cyclopenta[c]chromen-2-one (23)



To a solution of flavan **22** (847 mg, 1.91 mmol) in 18 mL of THF was added a solution of LiOH (230 mg, 9.58 mmol) in 9 mL of water. Add 8 mL of THF and 4 mL of water. After stirring for 1 hr, NaH_2PO_4 (9.6 mL of a 1 M solution in water, 9.6 mmol) was added followed by $NaIO_4$ (2.0 g, 9.35 mmol). After stirring for 1 hr, the solution was diluted with EtOAc. The aqueous solution was separated and extracted with EtOAc. The combined organic solutions were washed with 1:1 saturated aqueous Na_2SO_3:bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated to give 760 mg, 1.97 mmol, 100% of cyclopentanone **23**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 2H, J=8.8 Hz), 7.06 (d, 2H, J=8.7 Hz), 6.90-6.81 (m, 3H), 5.19 (s, 2H), 5.14-5.08 (m, 3H), 3.87 (t, 1H, J=7.5 Hz), 3.49 (s, 3H), 3.48 (s, 3H), 2.93 (m, 1H), 2.78 (dd, 1H, J=18.5, 8.4 Hz), 2.63 (d, 1H, J=18.5 Hz), 2.33 (dd, 1H, J=18.6, 12.1 Hz), 2.04 (dd, 1H, J=18.6, 8.1 Hz).

Example 8

Preparation of (3a*R*, 4*S*, 9b*S*)- and (3a*S*, 4*R*, 9b*R*)-8-Hydroxy-4-(4-hydroxy-phenyl)-1,3a,4,9b-tetrahydro-3H-cyclopenta[c]chromen-2-one



(3a*R*, 4*S*, 9b*S*)- and (3a*S*, 4*R*, 9b*R*)-8-Hydroxy-4-(4-hydroxy-phenyl)-1,3a,4,9b-tetrahydro-3H-cyclopenta[c]chromen-2-one (24)

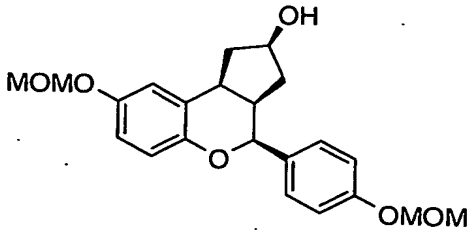
Stir a solution of cyclopentanone **23** (384 mg, 1.0 mmol) in 10 mL of THF and 8 mL of 3 M HCl overnight. Dilute the solution with EtOAc. Separate the aqueous solution and extract 2x with EtOAc. The combined organic solutions were washed with saturated aqueous sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated to afford 304 mg of cyclopentanone **24**. The material was purified by preparative chiral chromatography (Chiralpak AD, 65/35 heptane/ethanol).

Enantiomer A: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.34 min). HPLC (Chiralpak AD, 65/35 heptane/ethanol, 1mL/min; t_R = 4.1 min). LRMS(ES-) calcd for $C_{18}H_{15}O_4$: 295.10; found: 295.29 (M-H).

Enantiomer B: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.37 min). HPLC (Chiralpak AD, 65/35 heptane/ethanol, 1mL/min; t_R = 5.3 min). LRMS(ES-) calcd for $C_{18}H_{15}O_4$: 295.10; found: 295.29 (M-H).

Preparation 19

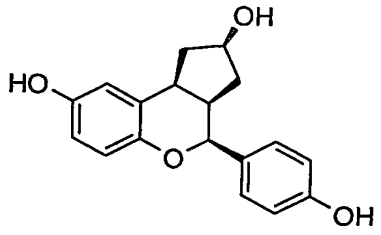
8-Methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-ol (25)



To a solution of cyclopentanon **23** (60 mg, 0.16 mmol) in 1 mL of MeOH and 0.5 mL of THF was added $NaBH_4$ (15 mg, 0.40 mmol). After stirring for 2 hrs saturated aqueous ammonium chloride was added. The solution was diluted with EtOAc. The aqueous solution was extracted 2x with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give 60 mg (0.16 mmol, 100%) of alcohol **25**. HRMS (ES+) calc for $C_{22}H_{30}NO_6$: 404.2073, found: 404.2082 ($M+NH_4$).

Example 9

Preparation of (2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2,8-diol



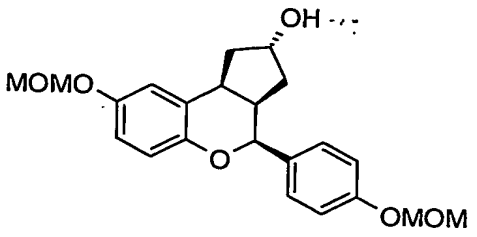
(2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2,8-diol (26)

Stir a solution of alcohol **25** (60 mg, 0.16 mmol) in 2 mL of THF and 2 mL of 3 M HCl overnight. Dilute the solution with EtOAc. Separate the aqueous solution and extract 2x with 10% MeOH in EtOAc. Wash the combined organic solutions with saturated aqueous sodium bicarbonate, brine, dry over Na_2SO_4, filter, and concentrate. Absorb to 1 g silica gel. Purify by silica gel chromatography (4 g silica gel, 0 to 10% MeOH/CH_2Cl_2 then 20% MeOH/CH_2Cl_2) to give 37 mg, (0.12 mmol, 79%) of alcohol

26. HPLC (Zorbax C18 column 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/min; t_r 7.79 min). LRMS(ES-) calcd for $C_{18}H_{15}O_4$: 297.11; found: 297.29 (M-H).

Preparation 20

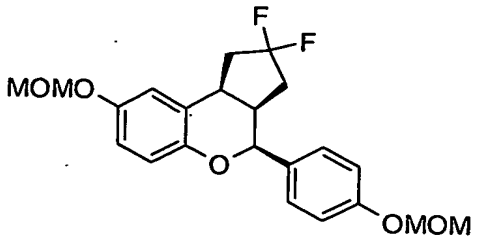
8-Methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-ol (27)



Cool a solution of alcohol **25** (50 mg, 0.13 mmol), triphenylphosphine (68 mg, 0.26 mmol), benzoic acid (24 mg, 0.2 mmol) to 0 °C. Add diisopropyl azodicarboxylate (50 ul, 0.26 mmol) slowly so that temperature of reaction does not rise above about 4 °C. After addition is complete, remove ice bath and warm the reaction to room temperature and stir overnight. Add MeOH to the reaction mixture and stir for 15 minutes before concentrating to a yellow oil. Purify by flash chromatography (10 g SiO_2, 40 mL/ min, 0 – 40% EtOAc/Hexanes over 20 minutes and 40% EtOAc/Hexane for 13 minutes) to yield 67 mg of a clear oil. To a solution of the clear oil (64 mg, 0.13 mmol) in THF:H_2O (1:1, 4 mL) add lithium hydroxide (4 mg, 0.13 mmol) and stir the reaction at room temperature overnight. Heat the mixture to 60 °C with stirring for 2 hours. Cool the mixture to room temperature and neutralize with 1.0 N HCl. Dilute with EtOAc and wash with saturated sodium bicarbonate and brine. Dry the organic solution (Na_2SO_4), filter and concentrate *in vacuo*. Purify by flash chromatography (10 g SiO_2, 40 mL/min, 0 – 70 % EtOAc/hexanes over 20 minutes and then 70% EtOAc/hexanes for 13 minutes) to give 41 mg (0.106 mmol, 82%) of alcohol **27** as a colorless oil. ^{1}H NMR (δ, 400 MHz, $CDCl_3$) 7.36 (d, 2H, *J*=8.8 Hz), 7.05 (d, 2H, *J*=8.8 Hz), 6.86-6.79 (m, 3H), 5.19 (s, 2H), 5.13 (d, 1H, J=6.8 Hz), 5.10 (d, 1H, 6.8 Hz), 5.07 (d, 1H, *J*=2.2 Hz), 4.32 (m, 1H), 3.65 (dt, 1H, *J*=3.5, 8.4 Hz), 3.50 (s, 3H), 3.49 (s, 3H), 2.99 (m, 1H), 2.27 (m, 1H), 2.07 (ddd, 1H, J=3.9, 5.6, 13.6), 1.87 (ddd, 1H, *J*=5.2, 11.6, 13.6 Hz), 1.42 (m, 1H), 1.27 (s, 1H). HRMS(ES+) calcd for $C_{22}H_{30}NO_6$: 404.2073; found: 404.2057 (M+NH_4).

Preparation 21

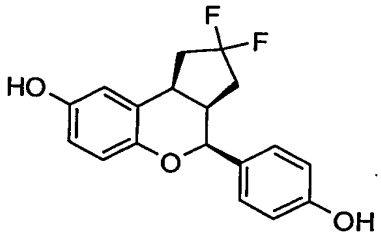
2,2-Difluoro-8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene (29)



Stir a solution of cyclopentanone **23** (273 mg, 0.710 mmol) in 0.5 mL of (diethylamino)sulfur trifluoride and 0.5 mL of dichloroethane in a 4 mL vial at 40 °C overnight. Dilute with CH_2Cl_2 and wash 2x with saturated aqueous sodium bicarbonate. Dry the organic solution over Na_2SO_4, filter, and concentrate. Absorb to 5 g of silica gel and purify by silica gel chromatography (35 g silica gel, 0 to 30% EtOAc/Hexanes over 48 min at 35 mL/min) to give 217 mg (0.53 mmol, 75%) of difluorocyclopentane **29**. ^1H NMR (δ, 400 MHz, $CDCl_3$) 7.34 (d, 2H, J=8.4 Hz), 7.06 (d, 2H, J=8.4 Hz), 6.90-6.83 (m, 2H), 6.80 (s, 1H), 5.19 (s, 2H), 5.13 (d, 1H, J=6.8 Hz), 5.11 (d, 1H, J=6.8 Hz), 5.02 (s, 1H), 3.67 (t, 1H, J=8.2 Hz), 3.49 (s, 6H), 2.89-2.67 (m, 2H), 2.40-2.09 (m, 2H), 1.88 (dt, 1H, J=14.3, 7.0 Hz).

Example 10

Preparation of (3a*R*, 4*S*, 9b*S*)- or (3a*S*, 4*R*, 9b*R*)-2,2-Difluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



(3a*R*, 4*S*, 9b*S*)- or (3a*S*, 4*R*, 9b*R*)-2,2-Difluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (30)

Stir a solution of difluorocyclopentane **29** (196 mg, 0.480 mmol) in 7 mL of THF and 3 mL of 3 M HCl overnight. Add 1 mL of 5 M HCl and let stir overnight. Dilute the solution with EtOAc. Separate the aqueous solution and extract 2x with EtOAc. The

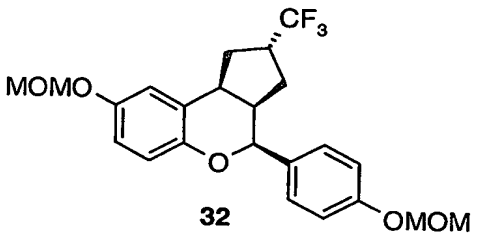
combined organic solutions were washed with saturated aqueous sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated. Absorb to 2 g of silica gel and purify by silica gel chromatography (10 g silica gel, 10 to 60% EtOAc/Hexanes over 30 min at 35 mL/min) to give 155 mg (0.48 mmol, 100%) of difluorocyclopentane **30**. The enantiomers were separated by preparative chiral chromatography (Chiralpak AD, 65/35 heptane/ethanol).

Enantiomer A: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.61 min). HPLC (Chiralpak AD, 20/80 IPA/ Heptane, 1mL/min; t_R = 8.8 min). HRMS(CI+) calcd for $C_{18}H_{17}F_2O_3$: 319.1146; found: 319.1151 (M+H).

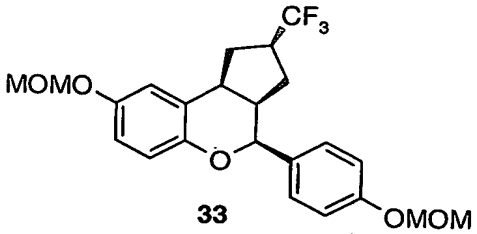
Enantiomer B: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.60 min). HPLC (Chiralpak AD, 20/80 IPA/ Heptane, 1mL/min; t_R = 16.0 min). HRMS(CI+) calcd for $C_{18}H_{17}F_2O_3$: 319.1146; found: 319.1164 (M+H).

Preparation 22

8-Methoxymethoxy-4-(4-methoxymethoxy-phenyl)-2-trifluoromethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene (32 and 33)



32



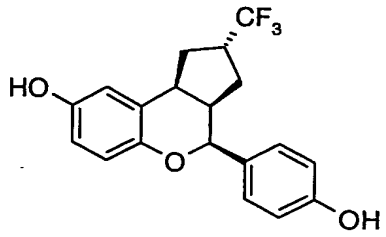
33

Add tetrabutylammonium fluoride (0.075 mL of a 1.0 M solution in THF, 0.075 mmol) to a solution of cyclopentanone **23** (288 mg, 0.75 mmol) and (trifluoromethyl)trimethylsilane (3.75 mL of a 0.5 M solution in THF, 1.875 mmol) in 5 mL of THF. After stirring for 2 hrs, add another 1.5 mL of (trifluoromethyl)trimethylsilane and 0.030 mL of tetrabutylammonium fluoride. After stirring for 1 hr, add another 0.75 mL of (trifluoromethyl)trimethylsilane and 0.015 mL of tetrabutylammonium fluoride. After stirring for 30 min, add saturated aqueous ammonium chloride. Extract the aqueous solution with EtOAc. Combine the organic solutions and wash with water, brine, dry over Na_2SO_4, filter and concentrate to an oil.

To a solution of the oil in 5 mL of THF add TBAF (0.75 mL of a 1.0 M solution in THF, 0.075 mmol). After stirring for 15 min add saturated aqueous sodium bicarbonate. Extract the aqueous solution with EtOAc. Combine the organic solutions and wash with water, brine, dry over Na_2SO_4, filter and concentrate to 350 mg of an oil which was used without further purification. To a solution of the oil, DMAP (10 mg, 0.08 mmol) and Et_3N (0.325 mL, 2.26 mmol) in 4 mL of dichloromethane add methyl chloroglyoxylate (0.105 mL, 1.14 mmol). After stirring for 1 hr, add another 0.16 mL of Et_3N and 0.050 mL of methyl chloroglyoxylate. After stirring for 30 min dilute the solution with EtOAc, wash with saturate aqueous sodium bicarbonate, brine, dry over Na_2SO_4, filter and concentrate. Absorb to 2 g of silica gel and purify by silica gel chromatography (10 g silica gel, 0 to 30% EtOAc/Hexanes over 20 min and then 30% EtOAc/Hexanes at 35 mL/min) to give 360 mg (0.67 mmol, 89%) of an oil which was used without further purification. A solution of the oil (320 mg, 0.59 mmol), triphenylsilane (625 mg, 1.78 mmol), and AIBN (15 mg, 0.091 mmol) in 6 mL of toluene was heated to 80 °C for 4 hrs. The solution was cooled to room temperature, filtered, and the precipitate washed with Et_2O. Combine the filtrates and concentrate. Absorb to 2 g of silica gel and purify by silica gel chromatography (35 g silica gel, 0 to 30% EtOAc/Hexanes over 48 min at 35 mL/min) to give 114 mg (0.26 mmol, 44%) of trifluoromethyl **32** and 136 mg (0.31 mmol, 52%) of trifluoromethyl **33**. The structures were assigned by 2D NMR spectroscopy (gDQCOSY, edited HSQC, and 2D-NOESY). Trifluoromethyl **32**: HRMS(FAB) calcd for $C_{23}H_{25}F_3O_5$: 438.1654; found: 438.1657 (M+H). Trifluoromethyl **33**: HRMS(FAB) calcd for $C_{23}H_{25}F_3O_5$: 438.1654; found: 438.1657 (M+H).

Example 11

Preparation of (2*S*, 3a*R*, 4*S*, 9b*S*)- and (2*R*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-2-trifluoromethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



(2*S*, 3a*R*, 4*S*, 9b*S*)- and (2*R*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-2-trifluoromethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (34)

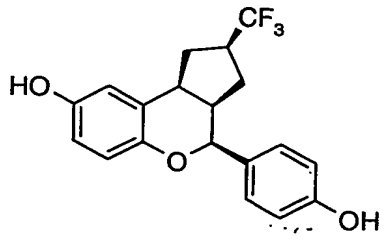
Stir a solution of trifluoromethyl **32** (105 mg, 0.240 mmol) in 4 mL of THF and 2 mL of 3 M HCl overnight. Add 1 mL of of THF and 0.5 mL of 12 M HCl. After stirring for 6 hrs, dilute the solution with EtOAc. Separate the aqueous solution and extract 2x with EtOAc. Wash the combined organic solutions with saturated aqueous sodium bicarbonate, brine, dry over Na_2SO_4, filter, and concentrate. Absorb to 2 g of silica gel and purify by silica gel chromatography (10 g silica gel, 0 to 40% EtOAc/Hexanes over 30 min at 35 mL/min) to give 62 mg (0.18 mmol, 74%) of trifluoromethyl **34**. The enantiomers were separated by preparative chiral chromatography (Chiralpak AD, IPA/heptane).

Enantiomer A: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.32 min). HPLC (Chiralpak AD, 30/70 IPA/ Heptane, 1mL/min; t_R = 2.53 min). HRMS(ES-) calcd for $C_{19}H_{16}F_3O_3$: 349.1052; found: 349.1059 (M-H).

Enantiomer B: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.32 min). HPLC (Chiralpak AD, 30/70 IPA/ Heptane, 1mL/min; t_R = 3.68 min). HRMS(ES-) calcd for $C_{19}H_{16}F_3O_3$: 349.1052; found: 349.1078 (M-H).

Example 12

Preparation of (2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-2-trifluoromethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



(2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-2-trifluoromethyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (35)

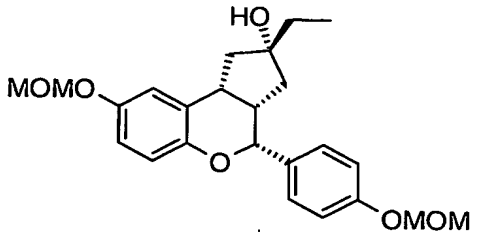
Stir a solution of trifluoromethyl **33** (125 mg, 0.290 mmol) in 4 mL of THF and 2 mL of 3 M HCl overnight. Add 1 mL of of THF and 0.5 mL of 12 M HCl. After stirring for 6 hrs, dilute the solution with EtOAc. Separate the aqueous solution and extract 2x with EtOAc. Wash the combined organic solutions with saturated aqueous sodium bicarbonate, brine, dry over Na_2SO_4, filter, and concentrate. Absorb to 2 g of silica gel and purify by silica gel chromatography (10 g silica gel, 0 to 50% EtOAc/Hexanes over 30 min at 35 mL/min) to give 92 mg (0.18 mmol, 91%) of trifluoromethyl **35**. The enantiomers were separated by preparative chiral chromatography (Chiralpak AD, IPA/heptane).

Enantiomer A: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.13 min). HPLC (Chiralpak AD, 30/70 IPA/ Heptane, 1mL/min; t_R = 2.96 min). HRMS(ES-) calcd for $C_{19}H_{16}F_3O_3$: 349.1052; found: 349.1086 (M-H).

Enantiomer B: HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.13 min). HPLC (Chiralpak AD, 30/70 IPA/ Heptane, 1mL/min; t_R = 4.66 min). HRMS(ES-) calcd for $C_{19}H_{16}F_3O_3$: 349.1052; found: 349.1064 (M-H).

Preparation 23

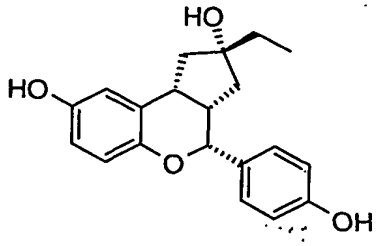
2-Ethyl-8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-ol (31)



Heat $CeCl_3$-$7H_2O$ (97 mg, 0.26 mmol) under vacuum at 70 °C for two hours and then warm slowly to 120 °C and continue heating overnight. Cool to room temperature and add THF (3 mL) followed by cyclopentanone **23** (100 mg, 0.26 mmol) and stir the solution for 45 minutes. Cool the reaction to –10 °C, add EtMgCl (3.0 M in THF, 87 ul, 0.26 mmol) and stir the reaction for 30 minutes. Quench the reaction with saturated aqueous NH_4Cl and extract with EtOAc (2X). Combine the organic extracts, wash with brine, dry (Na_2SO_4), filter and concentrate. Purify by flash chromatography (10 g silica gel, 40 mL/min, dry loading on 700 mg of silica gel, 0-30% EtOAc / hexanes for 20 minutes and 30 % EtOAc / hexanes for 13 minutes) to afford Alcohol **31** (86 mg, 0.207 mmol, 81 %). ^{1}H NMR (δ, 400 MHz, $CDCl_3$) 7.36 (d, 2H, *J*=8.8 Hz), 7.05 (d, 2H, *J*=8.8 Hz), 6.90-6.87 (m, 2H), 6.83 (dd, 1H, *J*=8.8, 2.6 Hz), 5.19 (s, 2H), 5.14 (d, 1H, J=6.8 Hz), 5.10 (d, 1H, J=6.8 Hz), 5.05 (d, 1H, *J*=2.2 Hz), 3.54 (dd, 1H, *J*=7.6, 7.6 Hz), 3.51 (s, 3H), 3.49 (s, 3H), 2.70 (ddd, 1H, J=2.2, 7.6, 9.6 Hz), 2.22 (dd, 1H, *J*=13.6, 7.9 Hz), 2.03 (d, 1H, J=13.6 Hz), 1.84 (dd, 1H, *J*=14.1, 10.1 Hz), 1.67 (dd, 1H, *J*=14.1, 9.2 Hz), 1.52 (m, 2H), 0.89 (t, 3H, *J*=7.3 Hz).

Example 13

Preparation of (2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-2-Ethyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b*R*-hexahydro-cyclopenta[c]chromene-2,8-diol

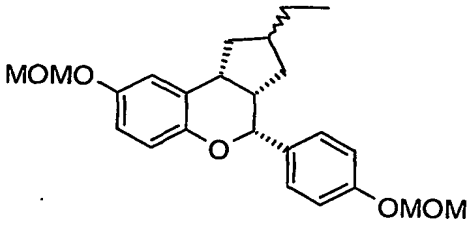


(2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-2-Ethyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2,8-diol (37)

Dissolve alcohol **36** (80 mg, 0.19 mmol) in THF (2 mL) and add 3 M HCl (2.0 mL). Stir the reaction at room temperature overnight. Dilute the reaction with EtOAc and wash with saturated aqueous sodium bicarbonate and brine. Extract the aqueous solutions with EtOAc (1X). Combine organic solutions, dry (Na_2SO_4), filter and concentrate *in vacuo*. Purify by flash chromatography (10 g SiO_2, dry loading on 700 mg silica gel, 40 ml/ min, 0-40% EtOAc/Hexane over 25 minutes and then 40 % EtOAc/hexane for 7 minutes) to afford alcohol **37** (20 mg, 0.061 mmol, 32%) as a white solid. HRMS(ES+) calcd for $C_{20}H_{23}O_4$: 327.1596; found: 327.1596 (M+H). HPLC (Zorbax C18 column;10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.6 min).

Preparation 24

2-Ethyl-8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene (38):

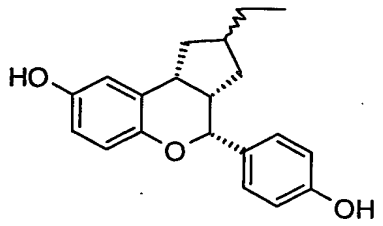


Prepare a solution of alcohol **31** (145 mg, 0.32 mmol), DMAP (5 mg, 0.035 mmol), and Et_3N (146 ul, 1.05 mmol) in CH_2Cl_2 (4 mL). Add methyl chloroglyoxylate (46 ul, 0.52 mmol) drop wise. Stir the reaction under N_2 for 30 minutes. Dilute with

EtOAc and wash with saturated aqueous sodium bicarbonate, 1.0 M HCl, saturated aqueous sodium bicarbonate and brine. Dry the organic solution over Na_2SO_4, filter, and concentrate *in vacuo*. Purification by flash chromatography (10 g SiO_2, 40 mL/min, dry loading on 500 mg silica, 0-30% EtOAc/Hexanes for 20 minutes and then 30 % EtOAc/Hexanes for 13 minutes) afforded 142 mg (0.28 mmol, 81%) of an oil which was used without further purification. Dissolve the oil (138 mg, 0.28 mmol) and triphenhyl tinhydride (290 mg, 0.83 mmol) in toluene (5 mL). Add AIBN (7 mg, 0.04 mmol) and heat the solution to 80 °C and stir for 18 hours. Filter the precipitate and wash with ether. Combine the filtrates, concentrate and purify by flash chromatography (10 g SiO_2, 40 mL/min, dry loading on 800 mg silica, 0- 30% EtOAc/Hexane over 20 minutes and then 30% EtOAc/hex for 13 minutes) to afford 107 mg (0.27 mmol, 99%) of alkyl cyclopentane **38** as a 4:1 mixture of diastereomers. HRMS(ES+) calcd for $C_{24}H_{34}NO_5$: 416.2437; found: 416.2432 ($M+NH_4$).

Example 14

Preparation of (2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*S*, 4*R*, 9b*R*)- and (2*S*, 3a*R*, 4*S*, 9b*S*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-2-Ethyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



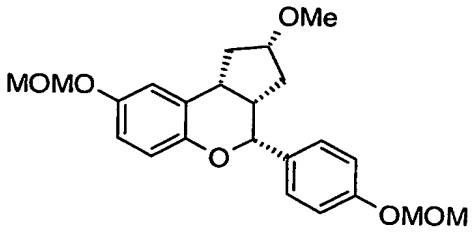
(2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*S*, 4*R*, 9b*R*)- and (2*S*, 3a*R*, 4*S*, 9b*S*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-2-Ethyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (39)

Dissolve alkyl cyclopentane **38** (109 mg, 0.27 mmol) in THF (4 mL) then add 3 M HCl (1.0 mL). Stir the reaction at room temperature overnight. Dilute the reaction with EtOAc and wash with saturated aqueous sodium bicarbonate and brine. Extract the aqueous layer with EtOAc (1X). Combine the organic extracts, dry (Na_2SO_4), filter and concentrate *in vacuo*. Purify by flash chromatography (10 g SiO_2, dry loading on 700 mg silica, 40 ml/ min, 0-30% EtOAc/Hexane over 25 minutes and then 30 % EtOAc/hexane

for 7 minutes) to afford 56 mg (0.18 mmol, 68%) of alkyl cyclopentane **39** as a white solid. HRMS(ES+) calcd for $C_{20}H_{26}NO_3$: 328.1913; found: 328.1906 ($M+NH_4$). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.33 min).

Preparation 25

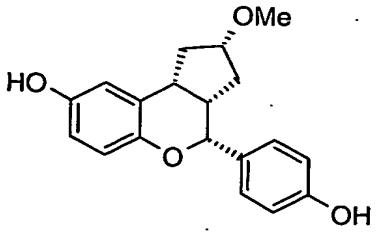
2-Methoxy-8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene (40)



To a solution of alcohol **25** (200 mg, 0.52 mmol) in DMF (5 mL) add sodium hydride (60% dispersion in mineral oil, 21 mg, 0.51 mmol) and stir the reaction at room temperature for 10 minutes. Cool the reaction to 0 °C and add methyl iodide (33 ul, 0.52 mmol) and stir the reaction mixture for 2 hours. Quench the reaction with saturated NH_4Cl and extract with EtOAc (2X). Combine the organic extracts and wash with H_2O, saturated aqueous sodium bicarbonate and brine. Dry (Na_2SO_4), filter and concentrate the solution *in vacuo*. Purify by flash chromatography (10 g SiO_2, 40 mL/ min, 0 – 40% EtOAc/Hexanes over 20 minutes and then 40% EtOAc/Hexanes for 13 minutes) to methyl ether **40** (210 mg, 0.52 mmol, 100%) as a yellow oil HRMS(ES+) calcd for $C_{23}H_{29}O_6$: 401.1964; found: 401.1969 (M+H).

Example 15

Preparation of (2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)- 4-(4-Hydroxy-phenyl)-2-methoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



(2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)- 4-(4-Hydroxy-phenyl)-2-methoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (41)

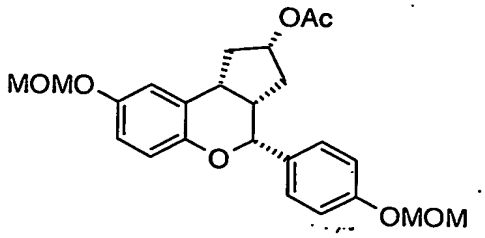
Dissolve methyl ether **40** (205 mg, 0.51 mmol) in THF (8 mL) and add 3M HCl (2 mL). Stir the reaction at room temperature overnight. Dilute the reaction with EtOAc and wash with saturated aqueous sodium bicarbonate and brine. Extract the aqueous solutions with EtOAc (1X). Combine the organic solutions, dry (Na_2SO_4), filter and concentrate them *in vacuo*. Purify the product by flash chromatography (10 g SiO_2, dry loading on 700 mg silica, 40 ml/ min, 0-50% EtOAc/Hexane over 20 minutes and then 50 % EtOAc/hexane for 13 minutes) to afford methyl ether **41** (125 mg, 0.4 mmol, 78%) as a white solid. HRMS(ES+) calcd for $C_{19}H_{23}NO_4$: 330.1705; found: 330.1695 ($M+NH_4$); HPLC (Zorbax C18 column;10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.95 min). The enantiomers wre separated by preparative chiral chromatography, chiralpol AD, IPA/Heptane.

Enantiomer A: HRMS(ES+) calcd for $C_{19}H_{24}NO_4$: 330.1705; found: 330.1691 ($M+NH_4$). HPLC (Chiralpak AD, 30-70% IPA/ Heptane for 15 min; 1mL/min; t_R = 3.52 min). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.95 min).

Enantiomer B: HRMS(ES+) calcd for $C_{19}H_{24}NO_4$: 330.1705; found: 330.1695 ($M+NH_4$). HPLC (Chiralpak AD, 30-80% IPA/ Heptane for 15 min; 1mL/min; t_R = 6.15 min). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.96 min).

Preparation 25

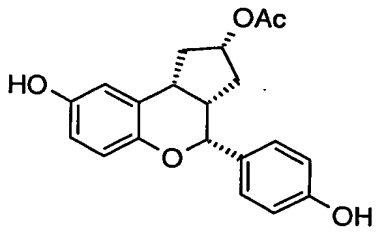
Acetic acid 8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-yl ester (42)



Add acetic anhydride (53 mg, 0.52 mmol) to a solution of alcohol **25** (200 mg, 0.52 mmol), Et_3N (0.14 mL, 1.03 mmol), and DMAP (6 mg, 0.052 mmol) in CH_2Cl_2 (5 mL) and stir the reaction at room temperature for 1 hour. Dilute the solution with EtOAc and wash with H_2O, saturated aqueous sodium bicarbonate and brine. Dry (Na_2SO_4), filter and concentrate the solution *in vacuo*. Purify the product by flash chromatography (10 g SiO_2, 40 mL/ min, 0 – 40% EtOAc/Hexanes over 20 minutes and then 40% EtOAc/Hexanes for 13 minutes) to afford acetate **42** (183 mg, 0.43 mmol, 83%) as a yellow oil. HRMS(FAB+) calcd for $C_{24}H_{28}O_7$: 428.1835; found: 428.1833 (M+).

Example 16

Preparation of (2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-Acetic acid 8-hydroxy-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-yl ester



(2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-Acetic acid 8-hydroxy-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-yl ester (43)

Dissolve acetate **42** (180 mg, 0.42 mmol) in THF (8 mL) and add 3M HCl (2 mL). Stir the reaction at room temperature overnight. Dilute the reaction with EtOAc and wash with saturated aqueous sodium bicarbonate and brine. Extract the aqueous solutions with EtOAc (1X). Combine, dry (Na_2SO_4), filter and concentrate the organic solutions *in vacuo*. Purify the product by flash chromatography (10 g SiO_2, dry loading on 700 mg

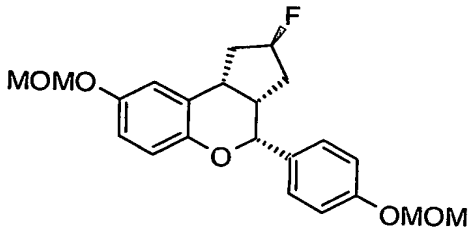
silica, 40 ml/ min, 0-50% EtOAc/Hexane over 20 minutes and then 50 % EtOAc/hexane for 13 minutes) to afford acetate **43** (47 mg, 0.14 mmol, 33%) as a white solid. The enantiomers were separated.

Enantiomer A: HRMS(ES+) calcd for $C_{20}H_{24}NO_5$: 358.1654; found: 358.1636 ($M+NH_4$). HPLC (Chiralpak AD, 20-80% IPA/ Heptane for 15 min; 1mL/min; t_R = 3.73 min). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.07 min).

Enantiomer B: HRMS(ES+) calcd for $C_{20}H_{24}NO_5$: 358.1654; found: 358.1641 ($M+NH_4$). HPLC (Chiralpak AD, 20-80% IPA/ Heptane for 15 min; 1mL/min; t_R = 5.35 min). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.07 min).

Preparation 26

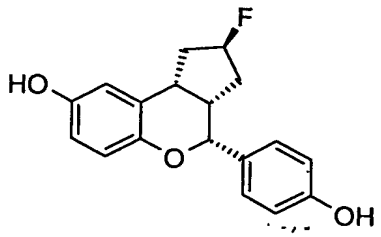
2-Fluoro-8-methoxymethoxy-4-(4-methoxymethoxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene (44)



Dissolve alcohol **25** (120 mg, 0.32 mmol) in CH_2Cl_2 (5 mL). Add N,N-diethyl amino sulfurtrifluride (0.8 mL, 6.0 mmol) and stir the reaction at room temperature overnight. Dilute the reaction with CH_2Cl_2 and wash with saturated aqueous sodium bicarbonate. Extract the aqueous layer with CH_2Cl_2 (1X). Combine the organic extracts, dry (Na_2SO_4), filter and concentrate them *in vacuo*. Purify the product by flash chromatography (10 g SiO_2, 40 mL/min, dry loading on 800 mg silica, 10- 30% EtOAc/hexane over 33 minutes) to afford flurorcyclopentane **44** (84 mg, 0.217 mmol, 70 %). HRMS(ES+) calcd for $C_{22}H_{26}FO_5$: 389.1764; found: 489.1761 (M+H).

Example 17

Preparation of (2*R*, 3a*S*, 4*R*, 9b*R*)- and (2*S*, 3a*R*, 4*S*, 9b*S*)-2-Fluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



(2*R*, 3a*S*, 4*R*, 9b*R*)- and (2*S*, 3a*R*, 4*S*, 9b*S*)-2-Fluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (45)

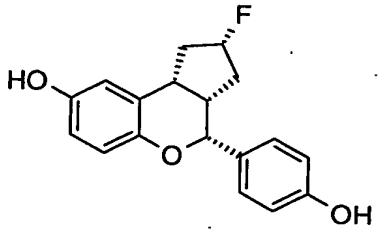
Dissolve fluorocyclopentane **44** (78 mg, 0.201 mmol) in THF (2 mL) and add 3M HCl (0.5 mL). Stir the reaction at room temperature overnight. Dilute the reaction with EtOAc and wash with saturated aqueous sodium bicarbonate and brine. Extract the aqueous solutions with EtOAc (1X). Combine the organic extracts, dry (Na_2SO_4), filter and concentrate them *in vacuo*. Purify the product by flash chromatography (10 g SiO_2, dry loading on 700 mg silica, 40 ml/ min, 0-30% EtOAc/Hexane over 20 minutes and then 30 % EtOAc/hexane for 13 minutes) to afford fluorocyclopentane **45** (54 mg, 0.18 mmol, 90%) as a white solid. The enantiomers were separated by preparative chiral chromatography (Chiralpak AD, IPA/heptane).

Enantiomer A: HRMS(ES+) calcd for $C_{18}H_{17}FO_3$: 301.1240; found: 301.1221 (M+H). HPLC (Chiralpak AD, 20-80% IPA/ Heptane for 15 min; 1mL/min; t_R = 5.88 min). HPLC (Zorbax C18 column;10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.46 min).

Enantiomer B: HRMS(ES+) calcd for $C_{18}H_{18}FO_3$: 301.1240; found: 301.1226 (M+H). HPLC (Chiralpak AD, 20-80% IPA/ Heptane for 15 min; 1mL/min; t_R = 7.13 min). HPLC (Zorbax C18 column;10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.49 min).

Example 18

Preparation of (2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-2-Fluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol

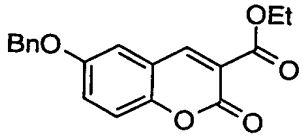


(2*S*, 3a*S*, 4*R*, 9b*R*)- and (2*R*, 3a*R*, 4*S*, 9b*S*)-2-Fluoro-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol (47)

Fluorocyclopentane **47** was prepared from alcohol **27** in a manner substantially similar to fluorocyclopentane **45**. HRMS(ES+) calcd for $C_{18}H_{18}FO_3$: 301.1240; found: 301.1241 (M+H).

Preperation 27

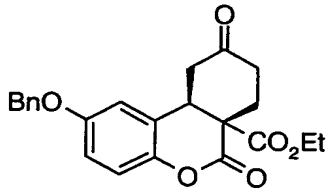
6-Benzyloxy-2-oxo-2H-chromene-3-carboxylic acid ethyl ester



To a 0 C solution of the phenol (26.7 g, 114 mmol) and benzyl bromide (20.5 mL, 171 mmol) in DMF (300 mL) add NaH (6.84 g, 1.5 mmol) portionwise over 15 min. Allow venting during the addition, during which time the solution turns dark red. After 30 min, remove the cooling bath and allow the solution to warm to 23 C, during which time a precipitate forms and the solution turns dark brown. After 2 h, slowly pour the solution into ½ satd. $NaHCO_3$ (500 mL), and filter the mixture. Wash the filter cake with H_2O (2 x 300 mL) and 50% Et_2O/hexanes (2 x 300 mL) to remove remaining aqueous salts and excess benzyl bromide. Dry the remaining yellow solid to afford Preparation 27 (28.9 g, 78%). ^1H NMR (d-DMSO) δ 8.67 (s, 1 H), 7.57 (s, 1 H), 7.37-7.47 (m, 7 H), 5.15 (s, 2 H), 4.28 (q, J = 7.2 Hz, 2 H), 1.31 (t, J = 7.2 Hz, 3 H).

Preparation 28

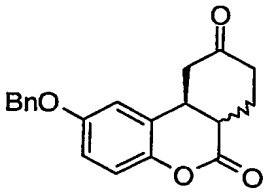
2-Benzyloxy-6,9-dioxo-8,9,10,10a-tetrahydro-7H-benzo[c]chromene-6a-carboxylic acid ethyl ester



Heat a suspension of Preparation 27, (12.0 g, 37.0 mmol), 2-trimethylsilyloxybutadiene (7.1 g, 55.5 mmol) and hydroquinone (0.040 g) in o-xylenes (40 mL) to 135 C for 24 h. Allow the reaction to cool to 23 C, then pour the contents into a solution of HOAc (5 mL) in TBAF (70 mL, 1 M in THF, 70 mmol). Stir the resulting solution for 1 hour at 23 C, then slowly pour the contents into ½ satd. $NaHCO_3$ (150 mL) and EtOAc (250 mL). Separate the layers and wash the organic extract with brine (150 mL), dry over Na_2SO_4, and concentrate to afford a brown semisolid. Purify the product by MPLC (0 to 15 to 30% EtOAc/hexanes) to afford Preparation 28 (9.3 g, 63%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.31-7.42 (m, 5 H), 7.04 (d, J = 8.8 Hz, 1 H), 6.90 (dd, *J* = 2.8, 8.8 Hz, 1 H), 6.73 (d, *J* = 2.8 Hz, 1 H), 5.03 (d, 2 H), 3.98-4.16 (m, 2 H), 3.66 (dd, *J* = 3.2, 13.2 Hz, 1 H), 2.88 (m, 1 H), 2.58-2.72 (m, 2 H), 2.49 (m, 1 H), 2.38 (t, *J* = 13.6 Hz, 1 H), 2.24 (td, *J* = 13.6, 5.2 Hz, 1 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

Preparation 29

2-Benzyloxy-7,8,10,10a-tetrahydro-6aH-benzo[c]chromene-6,9-dione

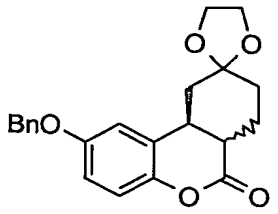


To a solution of Preparation 28 (9.25 g, 23.5 mmol) in THF (75 mL), EtOH (25 mL), and H_2O (40 mL) add lithium hydroxide hydrate (4.92 g, 117 mmol). Attach the flask to a reflux condenser and heat to 60 C for 1 h. Allow the contents to cool to 23 C and pour them into 1 N HCl and extract with Et_2O (2 x 75 mL) and EtOAc (2 x 75 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4, and concentrate to

afford the intermediate carboxylic acid as an off-white solid, which is used immediately in the next step.

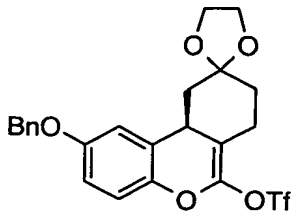
Add o-xylenes (100 mL) to the flask containing the crude acid, and heat the resulting heterogeneous solution to reflux for 2 h. Concentrate the mixture via rotary evaporator to afford Preparation 29 (approx. 9 g, ~quantitative) as an approximately 3:1 inseparable mixture of diastereomers. No further purification is required. ^{1}H NMR ($CDCl_3$) δ 7.30-7.44 (m, 5 H), 7.02 (d, J = 8.8 Hz, 1 H), 6.89 (dd, J = 8.8, 2.8 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 5.04 (s, 3 H), 3.02-3.36 (m, 2 H), 2.54-2.77 (m, 3 H), 2.36-2.45 (m, 2 H), 1.93-2.02 (m, 1 H).

Preparation 30



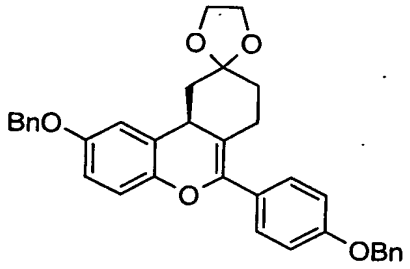
To a solution of Preparation 29 (~9 g, ~23 mmol) and ethylene glycol (2.79 mL, 50 mmol) in toluene (135 mL) add paratoluene sulfonic acid monohydrate (0.44 g, 2.3 mmol). Attach a Dean-Stark trap, and heat the solution to reflux for 2 h. Allow the solution to cool to 23 C, then pour the contents into ½ satd. $NaHCO_3$ (150 mL) and EtOAc (150 mL). Filter the mixture, and wash the filter cake with EtOAc and CH_2Cl_2. Separate the layers, and further extract the aqueous layer with EtOAc (100 mL) and CH_2Cl_2 (100 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4, and concentrate. Recrystallization from hexanes/toluene (9:1) followed by MPLC purification of the mother liquors (0 to 25 to 40% EtOAc/hexanes) affords Preparation 30 as an inseparable mixture of diastereomers (7.02 g, 82% over 3 steps). Note: Purification may be considered optional, as ^{1}H NMR of the crude product is fairly clean. ^{1}H NMR ($CDCl_3$) δ 7.30-7.44 (m, 5 H), 6.95 (d, J = 8.8 Hz, 1 H), 6.84 (dd, J = 8.8, 2.8 Hz, 1 H), 6.78 (d, J = 2.8 Hz, 1 H), 5.03 (s, 2 H), 3.98 (m, 4 H), 3.02-3.24 (m, 1 H), 2.30-2.90 (m, 2 H), 1.90-2.22 (m, 4 H), 1.54-1.67 (m, 1 H).

Preparation 31



To a –78 C solution of Preparation 30 (7.0 g, 19.1 mmol) in THF (80 mL) add potassium hexamethyldisilane (KHMDS) (53 mL, 0.5 M solution in toluene, 26.7 mmol) over 5 min. Add hexamethylphosphoramide (HMPA) (4.64 mL, 26.7 mmol) quickly, and stir the solution at –78 C for 25 min. Add a solution of N-phenyl triflamide (11.5 g, 32.2 mmol) in THF (15 mL + rinse) via syringe. Maintain the resulting solution at –78 C for 2 h, then pour the reaction contents into ½ satd. $NaHCO_3$ and extract with Et_2O (150 mL) and EtOAc (2 x 75 mL). Wash the combined organic extracts with H_2O (2 x 100 mL) and brine (100 mL), dry over Na_2SO_4, and concentrate. Purification of the crude product by MPLC (0 to 12 to 25% EtOAc/hexanes) affords Preparation 31 (6.25 g, 66%) as an off-white solid. ^1H NMR ($CDCl_3$) δ 7.25-7.43 (m, 5 H), 6.84 (d, J = 8.8 Hz, 1 H), 6.80 (dd, J = 8.8, 2.8 Hz, 1 H), 6.72 (d, J = 2.8 Hz, 1 H), 5.02 (s, 2 H), 4.04 (m, 4 H), 3.82 (dd, J = 4.4, 12.8 Hz, 1 H), 2.66 (dq, J = 14.0, 2.4 Hz, 1 H), 2.21 (m, 2 H), 1.91 (m, 1 H), 1.80 (t, J = 12.8 Hz, 1 H), 1.64 (td, J = 12.8, 4.4 Hz, 1 H).

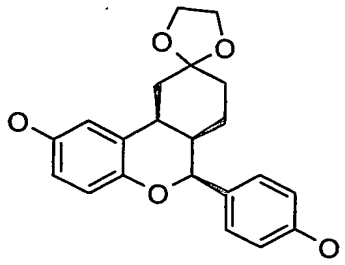
Preparation 32



Sparge N_2 (g) through a solution of Preparation 31 (3.0 g, 6.0 mmol), p-benzyloxyphenylboronic acid (1.65 g, 9.0 mmol), and LiCl (0.77 g, 18.1 mmol) in DME (40 mL) and aqueous Na_2CO_3 (7.5 mL, 2 M in H_2O, 15 mmol) for 15 min. Add palladium tetrakis triphenylphosphine (0.69 g, 0.60 mmol), then heat the solution to reflux for 24 h, during which time the product precipitates out as a white solid. Allow the

solution to cool to 23 C, then pour the contents into ½ satd $NaHCO_3$/ Et_2O and filter. Wash the filter cake with H_2O and cold Et_2O, affording 2.0 g of Preparation 32. Extract the filtrate with EtOAc (3 x 50 mL) and dry the combined organic extracts over Na_2SO_4 and concentrate to afford the remaining crude product. Purification of the crude material by silica gel chromatography (CH_2Cl_2) affords another 1.04 g. of Preparation 32. The total yield is 3.04 g (95%). ^1H NMR ($CDCl_3$) δ 7.31-7.47 (m, 12 H), 7.01 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 1 H), 6.77 (d, J = 8.8 Hz, 2 H), 5.11 (s, 2 H), 5.03 (s, 2 H), 3.98-4.12 (m, 4 H), 3.74 (dd, J = 12.8, 4.2 Hz, 1 H), 2.58 (m, 1 H), 2,24 (m, 1 H), 2.14 (td, J = 12.8, 4.2 Hz, 1 H), 1.85 (t, J = 12.8 Hz, 2 H), 1.58 (m, 1 H).

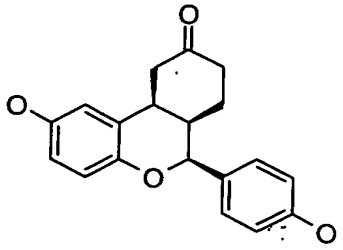
Preparation 33



To a mixture of 10 wt % Pd on carbon (0.5 g) in MeOH (100 mL) add a slightly soluble solution of Preparation 32 (3.0 g, 5.63 mmol) in THF (25 mL). Heat the solution to 40 C and maintain under 60 psi of H_2 (g) for 4 h. Filter the solution and concentrate the filtrate to afford Preparation 33 (~1.8 g crude, ~quantitative) as a white solid. ^1H NMR (CD_3OD) δ 7.22 (d, J = 8.8 Hz, 2 H), 6.77 (m, 3 H), 6.66 (d, J = 8.8 Hz, 1 H), 6.53 (dd, J = 3.2, 8.8 Hz, 1 H), 4.98 (s, 1 H), 3.88 (m, 1 H), 3.76 (m, 2 H), 3.68 (m, 1 H), 3.47 (m, 1 H), 2.48 (d, J = 14.8 Hz, 1 H), 1.99 (m, 1 H), 1.88 (dd, J = 14.8, 6.0 Hz, 1 H), 1.49-1.61 (m, 2 H), 1.37-1.46 (m, 1 H), 1.27 (m, 1 H), 1.17 (t, J = 7.2 Hz, 3 H).

Example 19

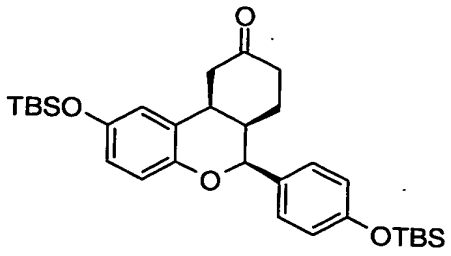
Preparation of (6S, 6aR, 10aS)-2-Hydroxy-6-(4-hydroxy-phenyl)-6,6a,7,8,10,10a-hexahydro-benzo[c]chromen-9-one



(6S, 6aR, 10aS)-2-Hydroxy-6-(4-hydroxy-phenyl)-6,6a,7,8,10,10a-hexahydro-benzo[c]chromen-9-one

To a solution of Preparation 33 (~1.7 g crude) in THF (40 mL) and H_2O (1 mL) add HCl solution (6 mL, 3 N in H_2O), and stir the mixture overnight. Pour the mixture into satd. $NaHCO_3$ and extract with Et_2O (2 x 50 mL) and EtOAc (2 x 50 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4, and concentrate to afford Example 19 (~1.3 g, ~quantitative) as a light yellow solid. This material is of suitable purity to be used crude for analogue development, but can be recrytallized from a variety of solvents (toluene/MeOH/hexanes or iPrOH/hexanes) for characterization. ^1H NMR (CD_3OD) δ 7.31 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.75 (d, J = 8.4 Hz, 2 H), 6.62 (dd, J = 8.8, 2.4 Hz, 1 H), 5.25 (s, 1 H), 3.89 (m, 1 H), 2.98 (m, 2 H), 2.58 (m, 1 H), 2.38 (m, 1 H), 2.13 (br d, J = 14.4 Hz, 1 H), 1.66 (m, 2 H).

Preparation 34

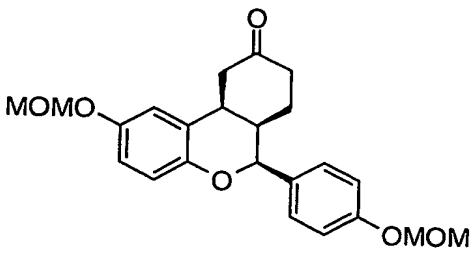


2-(tert-Butyl-dimethyl-silanyloxy)-6-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-6,6a,7,8,10,10a-hexahydro-benzo[c]chromen-9-one

To a solution of Example 19 (0.120 g, 0.39 mmol) and imidazole (0.079 g, 1.16 mmoL) in DMF (2.5 mL) add tert-butyldimethylsilyl chloride (0.131 g, 0.87 mmol). Allow the reaction to stir for 1 h, then pour into ½ satd. $NaHCO_3$ (50 mL) and extract with Et_2O (2 x 25 mL) and EtOAc (25 mL). Wash the combined organic extracts with H_2O (2 x 25 mL) and brine (25 mL), and dry the organics over Na_2SO_4. Concentrate the mixture, and purify the residue by MPLC (0% to 10% to 20% EtOAc/hexanes) to afford Preparation 34 (0.184 g, 88%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.63 (dd, J = 8.8, 2.8 Hz, 1 H), 5.27 (s, 1 H), 3.85 (m, 1 H), 3.01 (d, J = 15.2 Hz, 1 H), 2.79 (dd, J = 5.8, 15.2 Hz, 1 H), 2.45 (m, 1 H), 2.22 (m, 2 H), 1.60-1.80 (m, 2 H), 1.01 (s, 9 H), 0.99 (s, 9 H), 0.23 (s, 6 H), 0.21 (s, 3 H), 0.19 (s, 3 H).

Preparation 35

2-Methoxymethoxy-6-(4-methoxymethoxy-phenyl)-6,6a,7,8,10,10a-hexahydro-benzo[c]chromen-9-one

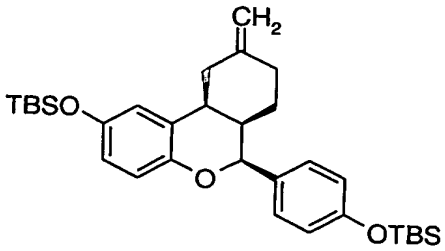


To a 0 C solution of Example 19 (0.100 g, 0.32 mmol) in THF (3 mL) add potassium tert-butoxide (0.090 g, 0.81 mmol) followed by methoxymethyl chloride

(MOM-Cl) (0.061 mL, 0.81 mmol). Remove the ice bath and stir for 1 h at room temperature. Pour the contents into ½ satd. $NaHCO_3$ (50 mL) and extract with Et_2O (2 x 25 mL) and EtOAc (2 x 25 mL). Wash the combine organic extracts with brine (50 mL), dry over Na_2SO_4, and concentrate to afford a brown residue. Purify the residue by MPLC (0% to 25% to 50% EtOAc/hexanes) to afford Preparation 35 (0.102 g, 80%). ^1H NMR ($CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 2 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.96 (d, J = 2.4 Hz, 1 H), 6.87 (dd, J = 2.4, 8.8 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 1 H), 5.28 (s, 1 H), 5.20 (s, 2 H), 5.13 (A of AB, J_{AB} = 7.0 Hz, 1 H), 5.07 (B of AB, J_{AB} = 7.0 Hz, 1 H), 3.87 (m, 1 H), 3.50 (s, 3 H), 3.48 (s, 3 H), 3.04 (br d, J = 14.4 Hz, 1 H), 2.79 (dd, J = 6.2, 14.4 Hz, 1 H), 2.46 (m, 1 H), 2.21 (m, 2 H), 1.62-1.79 (m, 2 H).

Preparation 36

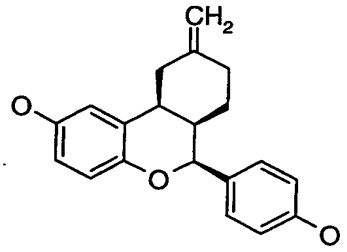
2-(tert-Butyl-dimethyl-silanyloxy)-6-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-9-methylene-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene



To a –40 C solution of Preparation 34 (0.100 g, 0.19 mmol) in THF (2 mL) and pyridine (0.045 mL) add the Tebbe reagent ($Cp_2ZrCl(H)Me$) (0.74 mL, 0.5 M toluene, 0.37 mmol). Maintain the reaction at –40 C for 1 h, then pour the contents into ½ satd. $NaHCO_3$ (50 mL) and extract with Et_2O (2 x 25 mL) and EtOAc (2 x 25 mL). Wash the combine organic extracts with brine (50 mL), dry over Na_2SO_4, and concentrate to afford a brown residue. Purify the residue by MPLC (0% to 5% to 10% EtOAc/hexanes) to afford Preparation 36 (0.093 g, 93%). ^1H NMR ($CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.75 (m, 2 H), 6.61 (dd, J = 2.4, 8.8 Hz, 1 H), 5.15 (s, 1 H), 4.62 (m, 2 H), 3.49 (br s, 1 H), 2.91 (d, J = 14.4 Hz, 1 H), 2.51 (dd, J = 14.4, 4.6 Hz, 1 H), 2.15 (m, 2 H), 1.92 (td, J = 12.8, 5.6 Hz, 1 H), 1.33 (m, 2 H), 1.01 (s, 18 H), 0.22 (s, 6 H), 0.19 (s, 3 H), 0.18 (s, 3 H).

Example 20

Preparation of (6aR, 6S, 10aS)-6-(4-Hydroxy-phenyl)-9-methylene-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol

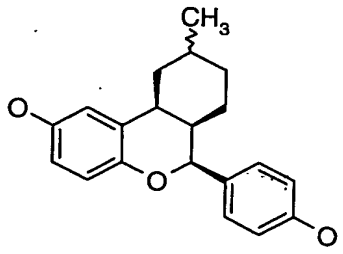


(6aR, 6S, 10aS)-6-(4-Hydroxy-phenyl)-9-methylene-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol

To a 0 C solution of Preparation 36 (0.093 g, 0.17 mmol) in THF (5 mL) add a solution of tetra-n-butyl ammonium fluoride (0.43 mL, 1 M in THF, 0.43 mmol). Stir the solution at 0 C for 1 h, then pour the contents into ½ satd. $NaHCO_3$ (50 mL) and extract with Et_2O (2 x 25 mL) and EtOAc (2 x 25 mL). Wash the combine organic extracts with brine (50 mL), dry over Na_2SO_4, and concentrate to afford a brown residue. Purify the residue by MPLC (0% to 25% to 40% EtOAc/hexanes) to afford Example 22 (0.028 g, 52%) as a white solid. ^1H NMR (CD_3OD) δ 7.26 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 6.79 (d, J = 3.2 Hz, 1 H), 6.69 (d, J = 8.4 Hz, 1 H), 6.57 (dd, J = 3.2, 8.4 Hz, 1 H), 5.09 (s, 1 H), 4.62 (m, 1 H), 3.48 (s, 1 H), 2.97 (d, J = 13.6 Hz, 1 H), 2.54 (dd, J = 5.2, 13.6 Hz, 1 H), 2.17 (m, 2 H), 1.95 (td, J = 5.2, 12.8 Hz, 1 H), 1.25-1.38 (m, 2 H).

Example 21

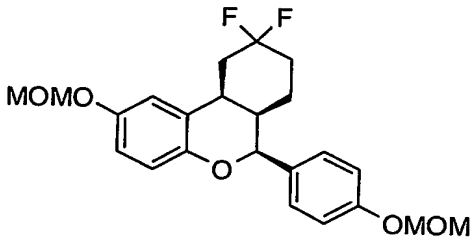
Preparation of (6aR, 6S, 9S, 10aS)-6-(4-Hydroxy-phenyl)-9-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol and (6aR, 6S, 9R, 10aS)-6-(4-Hydroxy-phenyl)-9-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol



(6aR, 6S, 9S, 10aS)-6-(4-Hydroxy-phenyl)-9-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol and (6aR, 6S, 9R, 10aS)-6-(4-Hydroxy-phenyl)-9-methyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol

To a mixture of 10 wt % Pd on carbon (0.03 g) in MeOH (20 mL) add a solution of Example 22 (0.022 g, 0.07 mmol) in MeOH (2 mL). Maintain the solution under 60 psi of H_2 (g) for 4 h. Filter the solution and concentrate the filtrate to afford Example 23 (0.022 g crude, 100%) as 3:1 ratio of epimers as a white solid. Major diastereomer: ^1H NMR (CD_3OD) δ 7.22 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 2.4 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.54 (dd, J = 8.8, 2.4 Hz, 1 H), 4.94 (s, 1 H), 3.30 (m, 1 H), 2.23 (d, J = 13.6 Hz, 1 H), 1.95 (m, 2 H), 1.33-1.56 (m, 3 H), 1.20 (m, 1 H), 1.11 (m, 1 H), 0.63 (d, J = 7.2 Hz, 3 H).

Preparation 37



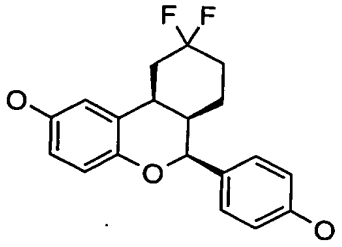
9,9-Difluoro-2-methoxymethoxy-6-(4-methoxymethoxy-phenyl)-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene

Heat a mixture of Preparation 35 (0.102 g, 0.26 mmol) and (Diethylamino) sulfur trifluoride (0.25 mL) in 1,2-dichloroethane (0.75 mL) to 40 C for 12 h. Purify the mixture by MPLC (0% to 10% to 25% EtOAc/hexanes) to afford Preparation 37 (0.042 g,

39%). ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 2 H), 7.08 (d, J = 8.8 Hz, 2 H), 7.02 (s, 1 H), 6.86 (m, 2 H), 5.20 (s, 2 H), 5.16 (s, 1 H), 5.15 (A of AB, J_{AB} = 6.4 Hz, 1 H), 5.11 (B of AB, J_{AB} = 6.4 Hz, 1 H), 3.66 (br s, 1 H), 3.50 (s, 6 H), 2.84 (m, 1 H), 1.96-2.23 (m, 3 H), 1.54-1.69 (m, 2 H), 1.44 (m, 1 H).

Example 22

Preparation of (6aR, 6S, 10aS)-9,9-Difluoro-6-(4-hydroxy-phenyl)-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol

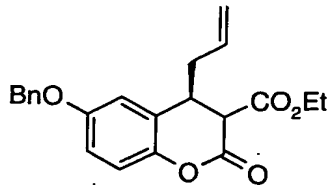


(6aR, 6S, 10aS)-9,9-Difluoro-6-(4-hydroxy-phenyl)-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-2-ol

Add a solution of HCl (2 mL, 3 N in H_2O) to Preparation 37 (0.042 g, 0.10 mmol) in THF (5 mL) and H_2O (1 mL) and stir the mixture for 12 h. Pour the mixture into satd. $NaHCO_3$ and extract with Et_2O (2 x 50 mL) and EtOAc (2 x 50 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4, and concentrate to afford the desired product as a light yellow solid. Purify the crude material by MPLC (0% to 25% to 40% EtOAc/hexanes) to afford Example 24 (0.014 g, 37%) as a yellow oil. ^{1}H NMR (CD_3OD) d 7.25 (d, J = 8.4 Hz, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 2.4 Hz, 1 H), 6.69 (d, J = 8.4 Hz, 1 H), 6.56 (dd, J = 2.4 Hz, 1 H), 5.07 (s, 1 H), 3.62 (br s, 1 H), 2.77 (m, 1 H), 2.09-2.28 (m, 2 H), 1.90 (m, 1 H), 1.47-1.65 (m, 2 H), 1.36 (m, 1 H).

Preparation 38

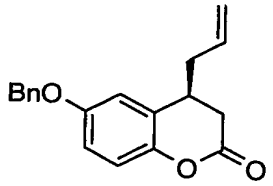
4-Allyl-6-benzyloxy-2-oxo-chroman-3-carboxylic acid ethyl ester



To a 0 C solution of Preparation 27 (10.0 g, 30.8 mmol) in THF (125 mL) add a solution of allyl magnesium chloride in Et_2O (46 mL, 1.0 M, 46 mmol). Maintain the reaction at 0 C for 30 min, then pour the reaction contents into a solution of ½ satd. $NaHCO_3$ (250 mL). Extract the solution with Et_2O (2 x 150 mL) and EtOAc (150 mL). Wash the combined organic extracts with H_2O (150 mL) and brine (150 mL), dry the organics over Na_2SO_4, and concentrate to afford a brown oil. Purify the product by MPLC (0% to 15% to 25% EtOAc/hexanes) to afford Preparation 38 (7.72 g, 68%) as a light yellow solid. ^1H NMR ($CDCl_3$) δ 7.31-7.43 (m, 5 H), 7.01 (d, J = 8.8 Hz, 1 H), 6.87 (dd, J = 8.8, 3.0 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 5.71 (m, 1 H), 5.15 (dd, J = 0.8, 9.8 Hz, 1 H), 5.10 (dd, J = 0.8, 17.6 Hz, 1 H), 5.04 (A of AB, J_{AB} = 14.2 Hz, 1 H), 5.03 (B of AB, J_{AB} = 14.2 Hz, 1 H), 4.08 (m, 2 H), 3.80 (d, J = 2.4 Hz, 1 H), 3.41 (m, 1 H), 2.35 (m, 2 H), 1.08 (t, J = 7.2 Hz, 3 H).

Preparation 39

4-Allyl-6-benzyloxy-chroman-2-one

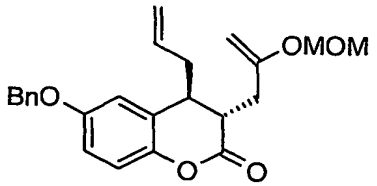


Heat a solution of Preparation 38 (4.8 g, 13.1 mmol) and LiOH (6 g) in a solution of THF (75 mL), EtOH (30 mL), MeOH (20 mL), and H_2O (50 mL) to 60 C for 2 h. Pour the contents into 1 N HCl (250 mL) and extract the mixture with Et_2O (2 x 200 mL) and EtOAc (2 x 150 mL). Wash the combined organic extracts with brine (200 mL), dry over Na_2SO_4, and concentrate to afford the crude β-keto acid.

Heat a solution of the crude acid in o-xylenes to reflux for 1.5 h. Remove the solvent in vacuo, and purify the lactone by MPLC (0% to 12% to 20% EtOAc/hexanes) to afford Preparation 39 (3.5 g, 91%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.31-7.44 (m, 5 H), 6.99 (d, J = 8.8 Hz, 1 H), 6.86 (dd, J = 8.8, 3.2 Hz, 1 H), 6.81 (d, J = 3.2 Hz, 1 H), 5.72 (m, 1 H), 5.07-5.14 (m, 2 H), 5.05 (s, 2 H), 3.03 (m, 1 H), 2.76 (t, J = 8.8 Hz, 2 H), 2.43 (m, 1 H), 2.30 (m, 1 H).

Preparation 40

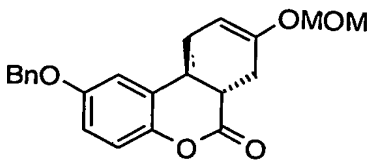
4-Allyl-6-benzyloxy-3-(2-methoxymethoxy-allyl)-chroman-2-one



Cool a solution of Preparation 39 (3.65 g, 12.4 mmol) in THF (90 mL) to –78 C. Add a solution of KHMDS (32 mL, 0.5 M in toluene, 16 mmoL) over 5 min, then allow to stir for 15 in at –78 C. Add hexamethylphosphoramide (HMPA) via syringe (2.8 mL, 16.1 mmoL) quickly, and allow to stir for 20 min at –78 C. Add 2-O-methoxylmethyl allyl iodide (4.24 g) over 2 min, and then allow the solution to warm to –50 C over 1.5 h. Pour the contents of the reaction into ½ satd. $NaHCO_3$ and extract with Et_2O (2 x 100 mL) and EtOAc (2 x 100 mL). Wash the combined organic extracts with H_2O (2 x 150 mL) and brine (150 mL) and then dry over Na_2SO_4. Concentrate the crude product to leave a brown oil, which is purified by MPLC (0% to 12% to 20% EtOAc/hexanes) to afford Preparation 40 (3.72 g, 76%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.31-7.44 (m, 5 H), 6.98 (d, J = 8.8 Hz, 1 H), 6.87 (dd, J = 8.8, 3.2 Hz, 1 H), 6.74 (d, J = 3.2 Hz, 1 H), 5.66 (m, 1 H), 5.01-5.09 (m, 4 H), 4.93 (A ob AB, J_{AB} = 6.4 Hz, 1 H), 4.90 (B of AB, J_{AB} = 6.4 Hz, 1 H), 4.18 (d, J = 2.4 Hz, 1 H), 3.87 (d, J = 2.4 Hz, 1 H), 3.44 (s, 3 H), 3.18 (m, 1 H), 2.86 (m, 1 H), 2.22-2.39 (m, 3 H), 2.12 (dd, J = 9.4, 14.0 Hz, 1 H).

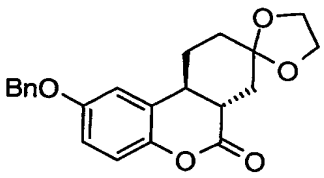
Preparation 41

2-Benzyloxy-8-methoxymethoxy-6a,7,10,10a-tetrahydro-benzo[c]chromen-6-one



Bubble N2 gas through a solution of Preparation 40 (1.0 g, 2.54 mmol) in CH_2Cl_2 (250 mL) equipped with a reflux condenser for 30 min. Add [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-tricyclohexylphosphine)ruthenium] (0.212 g, 0.25 mmol) and heat the reaction to reflux for 2.5 h. Allow the reaction to cool to room temperature, remove the condenser, and bubble air through the mixture for 10 min. Remove the solvent in vacuo, and purify the residue by MPLC (0% to 12% to 25% EtOAc/hexanes) to afford Preparation 41 (0.72 gm, 78%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.32-7.45 (m, 5 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.86 (m, 2 H), 5.05 (m, 3 H), 5.00 (A of AB, J_{AB} = 6.4 Hz, 1 H), 4.97 (B of AB, J_{AB} = 6.4 Hz, 1 H), 3.45 (s, 3 H), 2.94 (m, 1 H), 2.83 (m, 1 H), 2.56-2.70 (m, 3 H), 2.25 (m, 1 H).

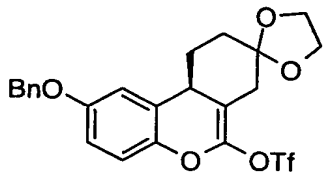
Preparation 42



Treat a solution of Preparation 41 (0.72 g, 1.97 mmol) in THF (40 mL) with 3 N HCl (3 mL) for 4 h. Pour the contents into H_2O and extract with Et_2O and EtOAc. Wash the combined organic extracts with satd. $NaHCO_3$ and brine, dry the combined extracts over Na_2SO_4, and concentrate to afford the crude intermediate ketone. Dissolve the ketone in toluene (40 mL) and add p-toluenesulfonic acid monohydrate (0.038 g), then attach a Dean Stark apparatus and heat the reaction to reflux for 2.5 h. Pour the contents into ½ satd. $NaHCO_3$ (50 mL) and separate the layers. Further extract the aqueous layer with Et2O and EtOAc (50 mL each). Wash the combined organic extracts with brine (50

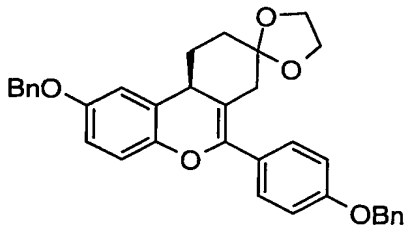
mL), dry the combined organics over Na2SO4, and concentrate to afford Preparation 42 (0.74 g, 100%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.31-7.44 (m, 5 H), 6.98 (d, J = 8.4 Hz, 1 H), 6.86 (m, 2 H), 5.04 (s, 2 H), 4.03 (m, 2 H), 3.94 (m, 2 H), 2.71 (m, 1 H), 2.55 (m, 1 H), 2.35-2.46 (m, 2 H), 1.92 (m, 1 H), 1.67-1.79 (m, 3 H).

Preparation 43



To a –78 C solution of Preparation 42 (0.366 g, 1.0 mmol) in THF (8 mL) add a solution of LDA (1.13 mL, 1.5 M cyclohexane, 1.7 mmol). Stir at –78 C for 15 min, then add HMPA (0.59 mL, 3.4 mmoL) and warm to –50 C. Stir for 15 min, then recool the solution to –78 C. Add a solution of N-phenyl triflamide (0.607 g, 1.7 mmol) in THF (2 mL) dropwise, and stir the resulting solution for 30 min. Pour the reaction contents into ½ satd. $NaHCO_3$, and extract the mixture with Et_2O (2 x 30 mL) and EtOAc (40 mL). Wash the combined organic extracts with H_2O (2 x 50 mL) and brine (50 mL), dry the organic layer over Na_2SO_4, and concentrate to afford the crude product. Purify the material by MPLC (0% to 15% to 25% EtOAc/hexanes) to afford Preparation 43 (0.059 g, 12%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.28-7.43 (m, 5 H), 6.81 (m, 2 H), 6.75 (d, J = 2.4 Hz, 1 H), 5.02 (s, 2 H), 3.99 (m, 4 H), 3.51 (q, J = 5.2 Hz, 1 H), 2.73 (dd, J = 2.8, 14.0 Hz, 1 H), 2.17 (m, 2 H), 1.83-1.97 (m, 3 H).

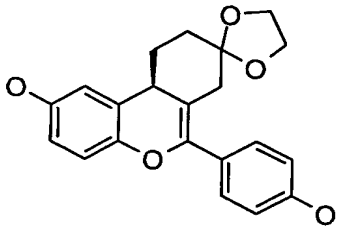
Preparation 44



Sparge N_2 (g) through a solution of Preparation 43 (0.059 g, 0.12 mmol), p-benzyloxyphenylboronic acid (0.038 g, 0.165 mmol), and LiCl (0.025 g, 0.60 mmol) in DME (2.5 mL) and aqueous Na_2CO_3 (0.25 mL, 2 M in H_2O, 0.5 mmol) for 15 min. Add

palladium tetrakis triphenylphosphine (0.035 g, 0.03 mmoL) and heat the solution to reflux for 24 h. Allow the solution to cool to 23 C, then pour the reaction contents into ½ satd $NaHCO_3$, and extract with EtOAc (3 x 25 mL). Combine the organic extracts and wash with brine (25 mL), then dry over Na_2SO_4 and concentrate. Purify the residue by MPLC (0% to 12% to 25% EtOAc/hexanes) to afford Preparation 44 (0.024 g, 38%) as a clear oil. ^1H NMR ($CDCl_3$) δ 7.31-7.47 (m, 10 H), 7.01 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.79 (s, 1 H), 6.75 (d, J = 8.8 Hz, 2 H), 5.11 (s, 2 H), 5.04 (s, 2 H), 3.97 (m, 4 H), 3.43 (m, 1 H), 2.64 (dd, J = 2.8, 14.0 Hz, 1 H), 2.20 (m, 1 H), 2.13 (m, 1 H), 1.99 (m, 1 H), 1.91 (m, 2 H).

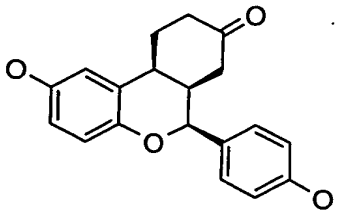
Preparation 45



To a mixture of 10 wt % Pd on carbon (0.02 g) in MeOH (25 mL) add a solution of Preparation 44 (0.020 g, 0.04 mmol) in THF (10 mL). Maintain the solution under 60 psi of H_2 (g) for 4 h. Filter the solution and concentrate the filtrate to afford Preparation 45 (0.012 g crude, ~quantitative) as a white solid. TLC R_f 0.4, 60% EtOAc/hexanes.

Example 23

Preparation of (6aR, 6S, 10aS)-2-Hydroxy-6-(4-hydroxy-phenyl)-6a,9,10,10a-tetrahydro-6H,7H-benzo[c]chromen-8-one

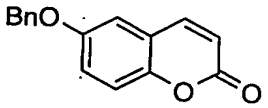


(6aR, 6S, 10aS)-2-Hydroxy-6-(4-hydroxy-phenyl)-6a,9,10,10a-tetrahydro-6H,7H-benzo[c]chromen-8-one

To a solution of Preparation 45 (0.012 g) in THF (20 mL) and H_2O (1 mL) add HCl solution (2 mL, 3 N in H_2O), and stir the mixture overnight. Pour the mixture into satd. $NaHCO_3$ and extract with Et_2O (2 x 50 mL) and EtOAc (2 x 50 mL). Wash the combined organic extracts with brine, dry over Na_2SO_4, and concentrate to afford crude Preparation 27 as a light yellow solid. Purify the crude material by MPLC (0% to 25% to 50% EtOAc/hexanes) to afford Example 25 (0.010 g, 90%) as a white solid. ^1H NMR (CD_3OD) δ 7.22 (d, J = 8.0 Hz, 2 H), 6.85 (m, 1 H), 6.79 (m, 3 H), 6.64 (m, 1 H), 5.22 (s, 1 H), 3.54 (m, 1 H), 2.67 (m, 1 H), 2.56 (m, 1 H), 2.26 (m, 2 H), 2.13 (m, 2 H), 1.84 (dd, J = 3.9, 14.5 Hz, 1 H).

Preparation 46

6-Benzyloxy-chromen-2-one



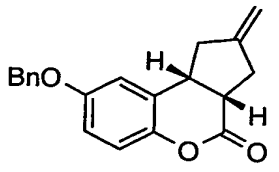
Equip a 5-L, three-neck, round-bottom flask with a large blade mechanical stirrer, thermocouple, an addition funnel, Claisen adapter, reflux condenser, and a sodium hydroxide scrubber. Charge the flask with 2,5-dimethoxycinnamic acid (182.3 g, 865 mmol, 1.0 equiv) and dichloroethane (2.5 L). Add boron tribromide (163.5 mL, 433.2 g, 1.73 mol, 2.0 equiv.) dropwise over 1 h, keeping the temperature below 35 °C. Gas evolution can be monitored as the temperature of the reaction is gradually increased to reflux (82 °C). Reflux for 12 h, cool to 5 °C, and quench by the careful addition of water (1.0 L). Filter the resulting yellow-red suspension/emulsion through a glass frit and wash

with dichloroethane (1.0 L) and heptane (1.0 L) to afford a brown solid. Dry the wet material in a vacuum oven (30 in., 35 °C) for 18 h, to afford the coumarin (180.3 g, 127% theory) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, J = 9.6 Hz, 1H), 7.22 (d, J = 9.9 Hz, 1H), 7.05 (m, 2H), 6.43 (d, J = 9.6 Hz, 1H).

Equip a 5-L, three-neck, round-bottom flask with a mechanical stirrer, thermocouple, an addition funnel, and an inlet adapter. Charge the flask with the coumarin prepared above (360.0 g, 2.20 mol, 1.0 equiv) and *N,N*-dimethylformamide (2.2 L). While keeping the temperature below 30 °C, add cesium carbonate [904.2 g, 2.78 mol, 1.25 equiv]. Then add benzyl bromide [475.5 g, 330.2 mL, 2.78 mol, 1.25 equiv] over a period of 1 h, keeping the temperature below 35 °C during the addition. Stir the mixture at ambient temperature (25–30 °C) for 10.5 h. Pour the reaction mixture into ice water (4.5 L), filter, and dry at ambient pressure for 72 h, triturate in heptane (1.5 L) with vigorous stirring, filter, and dry under reduced pressure (30 in., 35 °C) to afford preparation 46 (302.4 g, 1.20 mol, 60%) as a light brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (d, J = 9.6 Hz, 1H), 7.50–7.29 (m, 8H), 6.49 (d, J = 9.5 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 154.6, 147.9, 143.9, 136.6, 128.4, 127.9, 127.7, 119.9, 119.1, 117.3, 116.6, 111.9, 69.8; IR (KBr) 3052 (w), 1708 (s), 1568 (m), 1492 (w), 1444 (w), 1383 (w), 1272 (m), 1168 (w), 1110 (m), 1020 (m), 927 (w), 814 (w), 762 (w), 709 (w) cm^{-1}; HPLC analysis 95.9% (AUC), Phenomenex Luna C18(2) column; ESI MS *m/z* 253 $[C_{16}H_{12}O_3 + H]^+$

Preparation 47

8-Benzyloxy-2-methylene-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]chromen-4-one

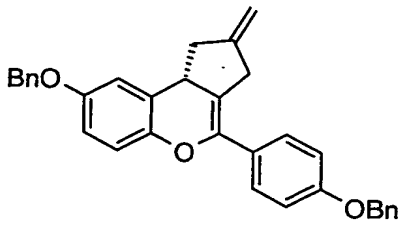


Starting from preparation 46 this compound can be prepared in a manner substantially similar to that described in preparation 13. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.32 (m, 5H), 6.98 (d, J = 8.8 Hz, 1H), 6.86 (dd, J = 3.1, 8.8 Hz, 1H), 6.82 (d, J =

3.1 Hz, 1H), 5.04 (s, 2H), 4.98-4.95 (m, 2H), 3.40 (dt, J = 7.5, 16.3 Hz, 1H), 3.15 (ddd, J = 4.4, 7.9, 11.9 1H), 3.06-3.01 (m, 1H), 2.82-2.72 (m, 2H), 2.47-2.40 (m, 1H).

Preparation 48

8-Benzyloxy-4-(4-benzyloxy-phenyl)-2-methylene-1,2,3,9b-tetrahydro-cyclopenta[c]chromene



Add p-benzyloxybromobenzene (20 g, 76 mmol) to magnesium metal (1.85 g, 76 mmol). Flush with nitrogen and add 76 mL of THF followed by a small crystal of I_2. Heat to reflux to initiate Grignard formation and then let stir at room temperature overnight. Add the resulting aryl Grignard via cannula to a solution of $ZnCl_2$ (76 mL of a 1 M solution in Et_2O, 76 mmol) in 152 mL of THF. Stir for 30 min and then let the precipitate settle to give a solution of the aryl zinc.

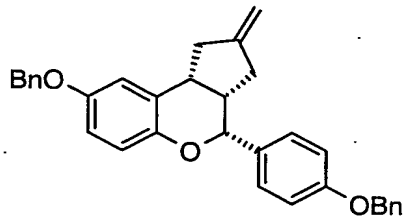
Cool a solution of preparation 47 (9.43 g, 30.8 mmol) in 312 mL of THF to –78 °C. Add KHMDS (74 mL of a 0.5 M solution in toluene, 37 mmol). Stir for 20 min. Add via cannula a solution of N-phenyl bis(trifluoromethanesulphonamide) (13.22 g, 37 mmol) in 47 mL of THF. Stir for 2 hrs and then quench with saturated aqueous NH_4Cl. Partition the solution between 250 mL of 1:1 water:brine and 250 mL of EtOAc. Separate and wash the organic solution with brine, dry over Na_2SO_4, filter, and concentrate. Adsorb the material to silica gel and purify by silica gel chromatography eluting with a linear gradient of 0-100% CH_2Cl_2 in hexanes to afford 9.77 g (22.3 mmol, 72%) of the enol triflate of preparation 46.

Add via cannula the solution of the aryl zinc described above to a solution of the enol triflate described above and $Pd(PPh_3)$ (2.57 g, 2.22 mmol) in 36 mL of THF under N_2. Heat the solution to 50 °C for 30 min. Cool the solution to room temperature and quench with saturated aqueous sodium bicarbonate and extract with EtOAc. Wash the combined organic solutions with brine, dry over Na_2SO_4, filter and concentrate. To remove the catalyst, dissolve the residue in 1:1 hexanes:CH_2Cl_2 and filter through celite.

Further purify the product by filtration through silica gel using 1:1 hexanes:CH_2Cl_2. Further purify by re-crystallization from EtOAc and hexanes to afford 5.96 g (12.6 mmol, 57%) of preparation 48. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.38 (m, 12H), 7.06-7.03 (m, 3H), 6.87 (dd, J = 2.6, 8.8 Hz, 1H), 6.79 (d, J = 3.1 Hz, 1H), 5.15 (s, 2H), 5.09 (s, 2H), 5.06 (s, 1H), 5.00 (s, 1H), 3.95 (t, J = 9.7 Hz, 1H), 3.48 (d, J = 20 Hz, 1H), 3.33 (d, J = 20 Hz, 1H), 3.12 (dd, J = 8.4, 15.4 Hz 1H), 2.50 (t, J = 12.8 Hz, 1H).

Preparation 49:

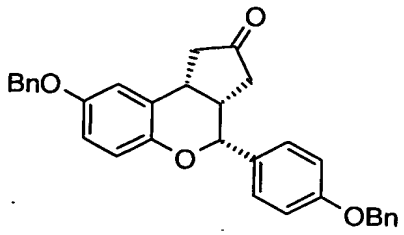
8-Benzyloxy-4-(4-benzyloxy-phenyl)-2-methylene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene



Add TFA (3.2 mL, 41.6 mmol) to a solution of preparation 48 (5.94 g, 12.6 mmol) and Et_3SiH (20.1 mL, 126 mmol) in 101 mL of CH_2Cl_2 at 0 °C. Stir for 5 min and then pour into a solution of saturated aqueous sodium bicarbonate. Wash the organic solution two times with saturated aqueous sodium bicarbonate, dry over Na_2SO_4, filter, and concentrate. Purify the product by silica gel chromatography eluting with 10-60% CH_2Cl_2 in hexanes to afford 3.67 g (7.73 mmol, 62%) of preparation 49. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.35 (m, 12H), 7.29-7.02 (m, 2H), 6.88 (d, J = 9.2 Hz, 1H), 6.83-6.79 (m, 2 H), 5.14 (d, J = 1.8 Hz, 1H), 5.12 (s, 2H), 5.05 (s, 2H), 4.78 (m, 2H), 3.60 (t, J = 7.5 Hz, 1H), 2.92 (m, 1H), 2.73 (m, 1H), 2.65 (d, J = 16.7 Hz, 1H), 2.46 (m, 1H), 2.13 (dd, J = 7.9, 16.7 Hz, 1H).

Preparation 50

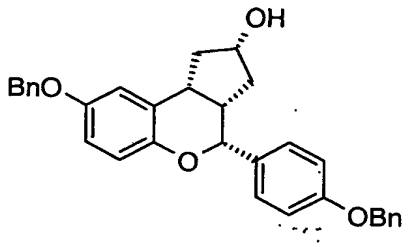
8-Benzyloxy-4-(4-benzyloxy-phenyl)-1,3a,4,9b-tetrahydro-3H-cyclopenta[c]chromen-2-one



Add osmium tetroxide (4.8 mL of a 2.5 wt% solution in t-BuOH, 0.38 mmol) to a solution of preparation 49 (3.62 g, 7.63 mmol), N-methylmorpholine (0.84 mL, 7.6 mmol), and N-methylmorpholine-N-oxide (1.79 g, 15.3 mmol) in 55 mL of THF and 21 mL of water. Stir for 6.5 hrs and then add 88 mL of THF, 106 mL of water and sodium periodate (8.16 g, 38.2 mmol). Stir overnight. Quench with an 1:1 solution of saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$. Separate the organic solution and wash with brine, dry over Na_2SO_4, filter and concentrate. Dissolve in 1:1 EtOAc:CH_2Cl_2 and wash with water, dry over Na_2SO_4, filter and concentrate to afford 3.35 g (7.03 mmol, 92%) of preparation 50. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.34 (m, 12H), 7.04-7.02 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 6.85 (dd, J = 2.6, 8.8 Hz, 1H), 6.77 (d, J = 2.6 H), 5.16 (s, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 3.90 (t, J = 7.5 Hz, 1H), 2.96 (dt, J = 3.0, 13.7 Hz, 1H), 2.80 (dd, J = 8.4, 18.5 Hz, 1H), 2.63 (d, J = 18.1 Hz, 1H), 2.37 (dd, J = 11.9, 18.9 Hz, 1H), 2.08 (dd, J = 7.9, 18.5 Hz, 1H).

Preparation 51

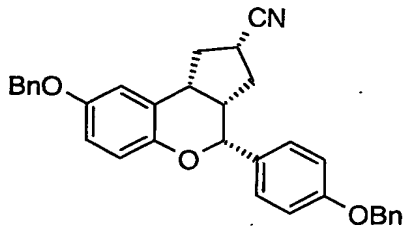
8-benzyloxy-4-(4-benzyloxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-2-ol



Add sodium borohydride (240 mg, 6.3 mmol) to a solution of preparation 50 (1.5 g, 3.15 mmol) in 30 mL of THF and 30 mL of methanol. Let stir for 30 min. Quench with saturated aqueous ammonium chloride, separate, back extract the aqueous solution two times with EtOAc. Combine the organic solutions and wash with 1:1 brine:water, dry over Na_2SO_4, filter, and concentrate to give 1.5 g (3.13 mmo, 99%) of preparation 51. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56-7.33 (m, 12H), 7.05-7.01 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 6.83-6.80 (m, 2H), 5.12 (s, 2H), 5.07 (s, 1H), 5.06 (s, 2H), 4.27 (d, J = 6.6, 11.0 Hz, 1H), 3.53 (m, 1H), 2.63 (m, 1H), 2.51 (dt, J = 7.5, 13.6 Hz, 1H),1.92-1.86 (m, 2H), 1.72 (dddd, J = 6.6, 11.0, 13.6, 17.1 Hz, 1H). HRMS (ES+) calc: 496.2488; found: 496.2485 $[M+NH_4]^+$.

Preparation 52

8-Benzyloxy-4-(4-benzyloxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2-carbonitrile

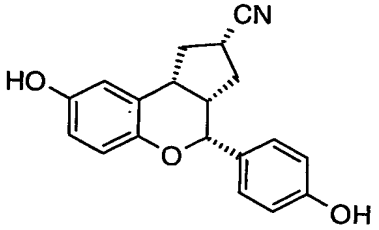


To a solution of preparation 51 (50 mg, 0.104 mmol), acetone cyanohydrin (48 µL, 0.52 mmol), and triphenyl phosphine (137 mg, 0.52 mmol), in 2.5 mL of THF at 0 °C add diisopropylazodicarboxylate (103 µL, 0.52 mmol). Stir the solution and allow it to warm slowly to room temperature overnight. Add 1 g of silica gel and concentrate. Purify by silica gel chromatography eluting with 10 - 30% EtOAc in hexanes to afford 30

mg (0.62 mmol, 59%) of preparation 52. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.33 (m, 12H), 7.06-7.02 (m, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.83 (dd, J = 3.1, 8.8 Hz, 1H), 6.77 (d, J = 3.1 Hz, 1H), 5.13 (s, 2H), 5.07 (d, J = 2.2 Hz, 1H), 5.06 (s, 2H), 3.70 (t, J = 6.6 Hz, 1H), 2.97 (ddt, J = 2.2, 9.2, 18.9 Hz, 1H), 2.68 (m, 1H), 2.43 (m, 1H), 2.28 (ddd, J = 1.8, 7.0, 8.8 Hz, 1H), 2.15 (dt, J = 9.2, 13.6 Hz, 1H), 1.80 (ddd, J = 6.2, 9.3, 13.6 Hz, 1H); HRMS(FAB) calcd. for $C_{33}H_{29}NO_3$: 487.2147; found: 487.2124 (M+).

Example 24

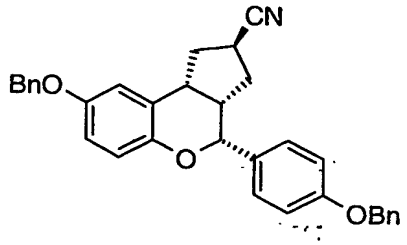
(2*R*, 3a*R*, 4*S*, 9b*S*)- and (2*S*, 3a*S*, 4*R*, 9b*R*)-8-Hydroxy-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2-carbonitrile



Dissolve preparation 52 (24 mg, 0.050 mmol) in 1 mL of THF. Add a slurry of 10% Pd/C (10 mg) in 1 mL of iPrOH. Add another 1 mL of THF, warm to redissolve preparation 52, then stir under an atmosphere of hydrogen gas at ambient pressure for 6 hrs. Filter the solution through a 0.2 μm HPLC filter, wash with methanol and concentrate. Purify by silica gel chromatography eluting with 5-50% (9:1 EtOAc:MeOH) in hexanes to afford 11.2 mg (0.036, 73%) of example 26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 2H), 6.85-6.82 (m, 2H), 6.76 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 2.6 Hz, 1H), 6.61 (dd, J = 3.0, 8.7 Hz, 1H), 5.00 (d, J = 2.5 Hz, 1H), 3.67 (t, J = 6.6 Hz, 1H), 2.99 (dt, J = 2.2, 9.7 Hz, 1H), 2.72 (ddd, J = 7.0, 9.7, 13.6 Hz, 1H), 2.41 (ddd, J = 7.0, 9.7, 12.7 Hz, 1H), 2.29 (ddd, J = 1.6, 6.6, 8.8 Hz, 1H), 2.11 (ddd, J = 9.2, 13.6, 18.0 Hz, 1H), 1.68 (ddd, J = 6.6, 9.2, 13.2 Hz, 1H). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.064 min). HRMS(ES-) calcd. for $C_{19}H_{16}NO_3$: 306.1130; found: 306.1155 (M-1).

Preparation 53

8-Benzyloxy-4-(4-benzyloxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2-carbonitrile



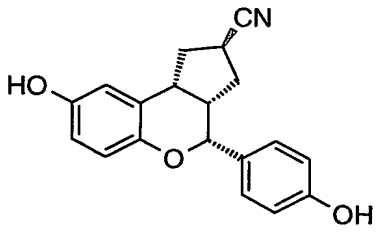
Place preparation 51 (0.2619 g, 0.5472 mmol) and triphenylphosphine (0.29 g, 1.1 mmol) in a flask and flush with N_2. Add THF (5.5 mL) and p-nitrobenzoic acid (0.27 g 1.6 mmol) and cool to 0 °C. Add diisopropylazodicarboxylate (0.22 mL, 1.1 mmol) dropwise to the reaction mixture keeping it below 5 °C. Let the reaction mixture warm slowly to room temperature overnight. Dilute the solution with EtOAc (100 mL), wash with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (50 mL), dry over Na_2SO_4, filter and concentrate. Purify by silica gel chromatography (10-25% of 9:1 CH_2Cl_2:EtOAc in hexanes over 30 min) to afford 0.1876 g (0.2989 mmol, 55 %) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 2H, J = 8.8 Hz), 8.71 (d, 2H, J = 8.8 Hz), 7.35-7.49 (m, 10 H), 7.41 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.8 Hz), 6.81-6.85 (m, 2H), 5.41 (m, 1H), 5.14 (m, 1H), 5.11 (s, 2H), 5.06 (s, 2H), 3.74-3.77 (m, 1H), 2.95-3.02 (m, 1H),2.49-2.55 (m, 1H), 2.36-2.42 (m, 1H), 2.16-2.24 (m, 1H), 1.73 (dd, 1H, J = 7.5 Hz, J = 14 Hz). HRMS (CI+) calcd. for $C_{39}H_{33}NO_7$: 627.2257; found: 627.2263 (M+).

Dissolve the yellow solid (0.1839 g, 0.2930 mmol) in 2.9 mL of THF and add an aqueous solution of LiOH (0.035 g, 1.5 mmol) in 1.1 mL of water. Stir at room temperature overnight. Add 1.0 *M* aqueous NaH_2PO_4 (1.5 mL, 1.5 mmol). Dilute with EtOAc (100 mL), wash with saturated aqueous $NaHCO_3$ (2 x 50 mL), wash with brine (50 mL), dry over Na_2SO_4, filter and concentrate to afford a white solid (0.1398 g, 0.2921 mmol, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.49 (m, 12H), 7.03 (d, 2H, J = 8.8 Hz), 6.87-6.89 (m, 1H), 6.78-6.80 (m, 2H), 5.12 (s, 2H), 5.10-5.11 (m, 1H), 5.05 (s, 2H), 4.34 (m, 1H), 3.65-3.70 (m, 1H), 2.98-3.06 (m, 1H),2.26-2.32 (m, 1H), 2.04-2.10 (m, 1H),1.87-1.95 (m, 1H), 1.44 (dd, 1H, J = 7.9 Hz, J = 14 Hz), 1.30 (m, 1H). HRMS (CI+) calcd. for $C_{32}H_{30}O_4$: 478.2144; found: 478.2154 (M+).

Dissove the white solid (0.1092 g, 0.2282 mmol) and PPh_3 (0.30 g, 1.1 mmol) in THF (5.5 mL). Add acetone cyanohydrin (0.42 mL, 4.6 mmol) and cool to 0 °C. Add diisopropyl azodicarboxylate (0.22 mL, 1.1 mmol) dropwise keeping the solution below 5 °C. Let the solution warm slowly to room temperature overnight. Add silica gel and concentrate. Purify by silica gel chromatography eluting with CH_2Cl_2 in EtOAc to afford 0.0432 g (0.0886 mmol, 39 %) of preparation 53. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.50 (m, 12H), 7.04 (d, 2H, J = 8.8 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.84 (dd, 1H, J = 8.8 Hz, J = 3.1 Hz), 6.76 (d, 1H, J = 3.1 Hz), 5.13 (s, 2H), 5.06 (s, 2H), 5.05 (m, 1H), 3.59-3.65 (m, 1H), 2.70-2.80 (m, 2H), 2.59-2.67 (m, 1H), 2.00-2.10 (m, 2H), 1.84-1.91 (m, 1H). HRMS calcd. for $C_{33}H_{29}NO_3$: 487.2147; found: 487.2134 (M+).

Example 25

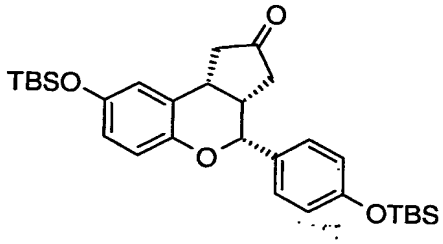
(2*S*, 3a*R*, 4*S*, 9b*S*)- and (2*R*, 3a*S*, 4*R*, 9b*R*)-8-Hydroxy-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene-2-carbonitrile



Example 27 can be prepared in a manner substantially similar to Example 26 except starting from Preparation 53. The hydrogenation is carried out under a 60 psi atmosphere of hydrogen for several days. ^1H NMR (δ, 400 MHz, $CDCl_3$): 7.30 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 6.78 (d, 2H, *J* = 8.8 Hz), 6.64-6.56 (m, 1H), 6.62 (dd, 1H, *J* = 8.4, 2.6 Hz), 4.99 (m, 1H), 3.55-3.62 (m, 1H), 2.90-3.00 (m, 1H), 2.67-2.76 (m, 2H), 1.94-2.04 (m, 2H), 1.78-1.94 (m, 2H). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 8.873 min). HRMS(CI+) calcd. for $C_{19}H_{17}NO_3$: 307.1208; found: 307.1212 [M+].

Preparation 54

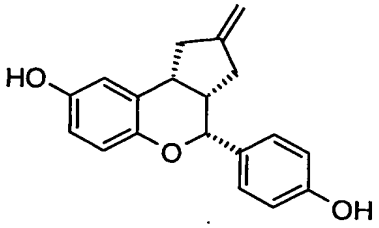
8-(tert-Butyl-dimethyl-silanyloxy)-4-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-1,3a,4,9b-tetrahydro-3H-cyclopenta[c]chromen-2-one



Dissolve Preparation 50 (1.59 g, 3.33 mmol) in 50 mL of THF. Add a slurry of 10% Pd/C (570 mg) in isopropyl alcohol. Stir the solution under 60 psi of hydrogen gas overnight. Filter the solution through celite and wash with isopropyl alcohol and THF. Combine and concentrate the organic solutions to afford a tan solid. Dissolve the solid 17 mL of DMF. Add imidazole (1.36 g, 20 mmol) and DMAP (42 mg, 0.34 mmol) followed by TBSCl (1.10 g, 7.3 mmol). Let the solution stir overnight. Dilute with EtOAc and wash with saturated aqueous sodium bicarbonate, water, brine, dry over Na_2SO_4, filter, and concentrate. Purify by silica gel chromatography eluting with 0-10% EtOAc in hexanes to afford 1.15 g (2.19, 66%) of preparation 54. ^{1}H NMR (400 MHz, MeOD): δ 7.33-7.30 (m, 2H), 6.90-6.87 (m, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.68 (dd, J = 2.2, 8.8 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 5.15 (d, J = 1.8 Hz, 1H), 3.87 (t, J = 7.5 Hz, 1H), 2.93 (m, 1H), 2.81 (dd, J = 7.6, 17.6 Hz, 1H), 2.62 (d, J = 18.5 Hz, 1H), 2.36 (dd, J = 12.3, 18.8 Hz, 1H), 2.04 (dd, J = 7.9, 18.8 Hz, 1H), 1.02 (s, 9H), 1.01 (s, 9H), 0.24 (s, 6H), 0.21 (s, 6H).

Example 26

(3a*R*, 4*S*, 9b*S*)- and (3a*S*, 4*R*, 9b*R*)-4-(4-Hydroxy-phenyl)-2-methylene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol

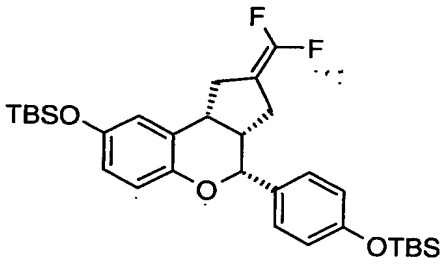


Add KHMDS (5.7 mL of 0.5 M solution in toluene, 2.85 mmol) to a solution of methyltriphenylphosphonium bromide (1.2 g, 3.36 mmol) in 30 mL of THF at –78 °C. Stir for 30 min and then add via cannula a solution of preparation 54 (500 mg, 0.95 mmol) in 10 mL of THF followed by 2x5 mL THF washes. Remove cooling bath and let stir overnight. Quench with saturated aqueous ammonium chloride. Dilute with EtOAc wash with 1:1 brine:water, brine, dry over Na_2SO_4, filter and concentrate. Adsorb to silica gel and purify by silica gel chromatography eluting with 0-100% EtOAc in hexanes to afford the title compound in addition to mono and di-TBS protected material. Repeat the procedure starting with 250 mg of preparation 54 except stir for only 3 hrs. Combine the di-TBS protected material (219 mg, 0.42 mmol) and dissolve in 5 mL of THF. Add TBAF (0.88 mL of a 1 M solution in THF, 0.88 mmol). Let stir for 15 min and quench with saturated aqueous sodium carbonate. Dilute with water and EtOAc. Separate and extract the aqueous solution with EtOAc. Combine the organic solutions, add a little methanol, and wash with brine, dry over Na_2SO_4, filter and concentrate. Repeat the same procedure with the combined mono-TBS protected material. Combine all the deprotected material and adsorb to 5 g of silica gel. Purify by silica gel flash chromatography eluting with 10-40% (9:1 EtOAc:MeOH) in hexanes to afford 255 mg (0.87 mmol, 75%) of example 28. The two enantiomers can be separated by chiral preparative HPLC (Chiralpak AD, MeOH) . ^{1}H NMR (400 MHz, MeOD): δ 7.32-7.29 (m, 2H), 6.84-6.80 (m, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 3.1 Hz, 1H), 6.58 (d, J = 3.1, 8.8 Hz, 1H), 5.05 (d, J = 1.8 Hz, 1H), 4.74 (d, J = 13.2 Hz, 2H), 3.54 (t, J = 7.5 Hz, 1H), 2.95-2.88 (m, 1H), 2.77-2.69 (m, 1H), 2.61 (d, J = 16.3 Hz, 1H), 2.40-2.32 (m, 1H), 2.05 (dd, J = 8.8, 16.7 Hz, 1H); HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.838 min; HRMS(ES-) calcd. for $C_{19}H_{17}O_3$:

293.1178; found: 293.1148 [M-1]. HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 9.0 min (enatiomer A); 13.4 min (enantiomer B).

Preparation 55

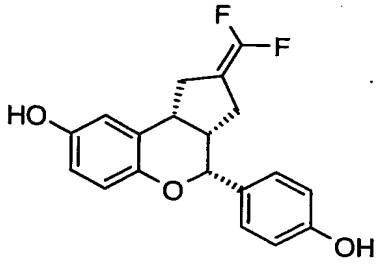
8-(tert-Butyl-dimethyl-silanyloxy)-4-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-2-difluoromethylene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene



Dissolve diisopropylamine (67 µL, 0.48 mmol) in 2 mL of THF, cool to –50 °C and add n-butyllithium (238 µL of a 1.6 M solution in hexanes, 0.38 mmol). Then add a solution of (Difluoromethyl)diphenylphosphine oxide (prepared according to Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T.; Matthews, D. P.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5571-5574) in 0.5 mL of THF via cannula followed by a 0.5 mL wash. Let stir for 30 min and then add preparation 54 (100 mg, 0.19 mmol) as a solution in 0.5 mL of THF via syringe followed by a 0.5 mL wash. Let stir and allow to warm slowly to 0 °C over 2 hrs. Remove the cooling bath and let warm to room temperature and then warm to reflux for 1 hr. Cool the solution to room temperature and quench with saturated aqueous ammonium chloride. Dilute the solution with EtOAc, wash with brine, dry over Na_2SO_4, filter and concentrate. Adsorb to 1 g of silica gel and purify by silica gel chromatography eluting with 5-20% EtOAc to afford 41 mg (0.073 mmol, 39%) preparation 55. ^{1}H NMR (400 MHz, MeOD): δ 7.35-7.30 (m, 2H), 6.91-6.88 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.69-6.65 (m, 2H), 5.14 (s, 1H), 3.60 (m, 1H), 2.82 (m, 1H), 2.74-2.64 (m, 2H), 2.42 (m, 1H), 2.09 (dd, J = 8.3, 15.8 Hz, 1H), 1.03 (s, 9H), 1.02 (s, 9H), 0.24 (s, 6H), 0.22 (s, 6H).

Example 27

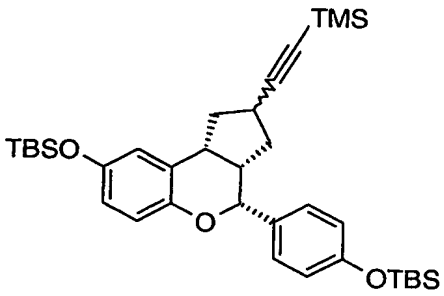
(3a*R*, 4*S*, 9b*S*)- and (3a*S*, 4*R*, 9b*R*)-2-Difluoromethylene-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Add TBAF (135 μL of a 1M solution in THF, 0.135 mmol) to a solution of preparation 55 (38 mg, 0.068 mmol) in 1 mL of THF. Let stir for 5 min, add one more drop of TBAF and then quench with aqueous sodium bicarbonate. Dilute with EtOAc, wash with water, brine, dry over Na_2SO_4, filter and concentrate. Adsorb to 0.5 g of silica gel and purify by silica gel chromatography eluting with 5-50% (9:1 EtOAc:MeOH) in hexanes to afford 20 mg (0.061 mmol, 89%) of example 29. ^{1}H NMR (400 MHz, MeOD): δ 7.31 (m, 2H), 6.83 (m, 2H), 6.74 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 6.61 (dd, J = 2.6, 8.8 Hz, 1H), 5.07 (s, 1H), 3.60 (m, 1H), 2.86-2.73 (m, 2H), 2.64 (d, J = 15.4 Hz, 1H), 2.34 (m, 1H), 2.04 (m, 1H); HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.094 min; HRMS(ES-) calcd. for $C_{19}H_{15}F_2O_3$: 329.0989; found: 329.0999 [M-1].

Preparation 56

8-(tert-Butyl-dimethyl-silanyloxy)-4-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-2-trimethylsilanylethynyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene



Add 1 mL of dry THF to dry cerium trichloride (120 mg, 0.22 mmol, prepared from cerium trichloride heptahydrate according to cerium(III) chloride in the

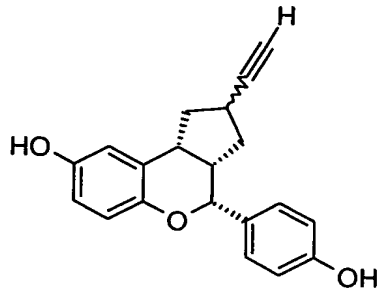
Encyclopedia of Reagents for Organic Synthesis, Wiley Interscience), stir for 1 hr, and then cool to 0 °C. In a separate flask add n-butyllithium (0.286 mL of a 1.6 M solution in hexanes, 0.46 mmol) to a solution of trimethylsilylacetylene (80 □L, 0.57 mmol) in 1 mL of THF cooled to –78 °C. Add this solution to the cerium trichloride via cannula. Then add via cannula a solution of preparation 54 (120 mg, 0.22 mmol) in 1 mL of THF followed by 2x0.5 mL THF washes. Let stir for 3 hrs. Prepare another solution of lithiated trimethylsilylacetylene as described above and add it to the reaction flask via cannula. Let stir for 1 hr. Quench the reaction with saturated aqueous ammonium chloride, dilute with EtOAc, separate and extract the aqueous solution with EtOAc. Combine the organic solutions and wash with water, brine, dry over Na_2SO_4, filter and concentrate.

Dissolve the material in 2 mL of CH_2Cl_2. Add DMAP (3 mg, 0.024 mmol), triethylamine (0.096 mL, 0.69 mmol), and then add methylchlorooxoacetate (0.032 mL, 0.34 mmol). Let stir for 1 hr. Quench with saturated sodium bicarbonate and separate. Wash the organic solution with 1 M aqueous NaH_2PO_4, saturated aqueous sodium bicarbonate, brine, dry over Na_2SO_4, filter and concentrate. Adsorb to 1 g of silica gel and purify by silica gel flash chromatography eluting with 0-15% EtOAc in hexanes.

Dissolve the material in 1.5 mL of toluene. Add triphenyltin hydride (163 mg, 0.464 mmol) and AIBN (4 mg, 0.024 mmol). Warm the solution to 80 °C. Let stir for 1 hr. Remove heat and let sit for 3 hrs. Filter through a glass frit and wash precipitate with ether. Combine the filtrates and concentrate. Adsorb to 1.2 g of silica gel and purify by silica gel chromatography eluting with 0-50% CH_2Cl_2 in hexanes to afford 56 mg (0.092 mmol) of preparation 56 as a 5:1 diastereomeric mixture of products. ^{1}H NMR (400 MHz, $CDCl_3$) of major diastereomer: δ 7.37-7.27 (m, 2H), 6.89-6.85 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.65-6.60 (m, 2H), 4.98 (d, J = 2.2 Hz, 1H), 3.49 (m, 1H), 2.75-2.50 (m, 3H), 1.81-1.66 (m, 3H), 1.03 (s, 9H), 1.02 (s, 9H), 0.24 (s, 6H), 0.22 (s, 6H), 0.10 (s, 9H).

Example 28

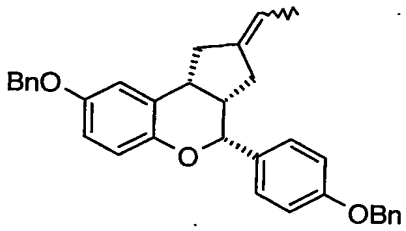
(3a*R*, 4*S*, 9b*S*)- and (3a*S*, 4*R*, 9b*R*)-2-Ethynyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Add TBAF (0.28 mL of a 1 M solution in THF, 0.28 mmol) to a solution of preparation 56 (56 mg, 0.092 mmol) in 2 mL of THF. Let stir for 10 min. Quench with saturate sodium bicarbonate and dilute with EtOAc. Separate and wash the organic solution with water, brine, dry over Na_2SO_4, filter and concentrate. Adsorb to 0.5 g silica gel. Purify by silica gel chromatography eluting with 0-50% (9:1 EtOAc:MeOH) in hexanes to afford 11.3 mg (0.037 mmol) of example 30 as a 5:1 mixture of diastereomers. ^{1}H NMR (400 MHz, MeOD) of major diastereomer: δ 7.27 (m, 2H), 6.83-6.81 (m, 2H),6.74 (d, J = 8.0 Hz, 1H), 6.64-6.56 (m, 2H), 4.89 (d, J = 3.1 Hz, 1H), 3.48 (dt, J = 8.8, 5.7 Hz, 1H), 2.74-2.57 (m, 3H), 2.22 (d, J = 2.6 Hz), 1.64-1.57 (m, 3H); HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 9.683 min (major), 9.805 (minor); HRMS(ES-) calcd. for $C_{20}H_{17}O_3$: 305.1178; found: 305.1170 [M-1].

Preparation 57

8-Benzyloxy-4-(4-benzyloxy-phenyl)-2-ethylidene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene

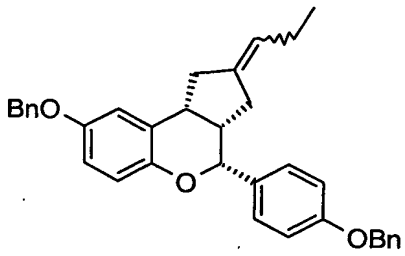


Heat a solution of preparation 50, (0.1562 g, 0.3278 mmol) in dry THF (6 mL) to dissolve. Cool a solution of ethyltriphenylphosphonium bromide (0.49 g, 1.3 mmol) in

dry THF (10 mL) to – 78 °C and then add KHMDS (2.2 mL of a 0.5 M solution in toluene, 1.1 mmol). After stirring at – 78 °C for 15 min, add the solution of preparation 50 dropwise via cannula. Allow the solution to warm to RT for 2h, then quench with saturated aqueous ammonium chloride (25 mL) and water (25 mL) and extract with EtOAc (3 x 50 mL). Wash the combined organic solutions with brine (50 mL), dry over Na_2SO_4, filter and concentrate. Purify by silica gel flash chromatography eluting with 0-50% CH_2Cl_2 in hexanes to afford 0.1552 g (0.3179 mmol, 97 %) of preparation 57 as mixture of E and Z isomers. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.50 (m, 12H, 2 isomers), 7.02-7.06 (m, 2H, 2 isomers), 6.78-6.89 (m, 4H, 2 isomers), 5.22 (m, 1 H, 2 isomers), 5.17 (d, 1H, J = 1.8 Hz, 1 isomer), 5.15 (d, 1H, J = 1.3 Hz, 1 isomer), 5.13 (s, 2H, 1 isomer), 5.12 (s, 2H, 1 isomer), 5.06 (s, 2H, 1 isomer), 5.05 (s, 2H, 1 isomer), 3.63 (t, 1H, J = 7.9 Hz, 1 isomer), 3.54 (t, 1H, J = 7.0 Hz, 1 isomer), 2.60-2.85 (m, 3H, 2 isomers), 2.41-2.48 (m, 1H, 1 isomer), 2.25-2.32 (m, 1H, 1 isomer), 2.03-2.12 (m, 1H, 2 isomers), 1.52 (d, 3H, J = 6.6 Hz, 1 isomer), 1.47 (d, 3H, J = 7.0 Hz, 1 isomer). HRMS(CI+) calcd. for $C_{34}H_{33}O_3$: 489.6241; found: 489.2411 (M+1).

Preparation 58

8-Benzyloxy-4-(4-benzyloxy-phenyl)-2-propylidene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene

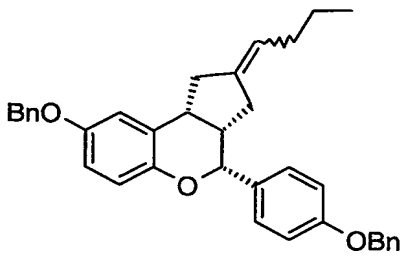


Preparation 58 can be prepared in a manner substantially similar to preparation 57 starting with preparation 50 (0.2041g, 0.4283 mmol) and propyltriphenyl-phosphonium bromide to obtain 0.1927g (0.3834 mmol, 90 %) of a mixture of *E* and *Z* isomers. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.50 (m, 12H, 2 isomers), 7.02-7.06 (m, 2H, 2 isomers), 6.79-6.89 (m, 4H, 2 isomers), 5.16 (m, 1H, 1 isomer), 5.145 (m, 1H, 1 isomer), 5.13 (s, 2H, 1 isomer), 5.12 (s, 2H, 1 isomer), 5.06 (s, 2H, 1 isomer), 5.05 (s, 2H, 1 isomer), 3.62 (t, 1H, J = 7.5 Hz),3.54 (t, 1H, J = 7.0 Hz, 1 isomer), 2.58-2.92 (m, 3H, 2 isomers), 2.41-

2.48 (m, 1H, 1isomer), 2.25-2.32 (m, 1H, 1 isomer), 1.85-2.11 (m, 3H, 2 isomer), 0.896 (t, 3H, J = 7.5 Hz, 1-isomer), 0.863 (t, 3H, J = 7.5 Hz, 1 isomer). HRMS(CI+) calcd. for $C_{35}H_{35}O_3$: 503.2586; found: 503.2563 (M+1) .

Preparation 59

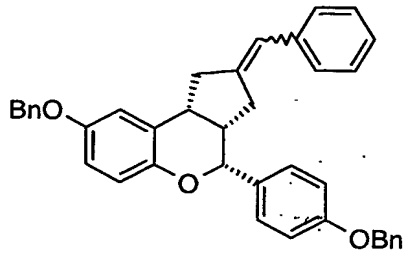
8-Benzyloxy-4-(4-benzyloxy-phenyl)-2-butylidene-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene



Preparation 59 can be prepared in a manner substantially similar to preparation 57 starting with preparation 50 (0.203 g, 0.427 mmol) and butyltriphenyl-phosphonium to obtain (0.1894 g, 0.3665 mmol, 86 %) of a mixture of *E* and *Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.50 (m, 12H, 2 isomers), 7.02-7.06 (m, 2H, 2 isomers), 6.78-6.88 (m, 4H, 2 isomers), 5.14 –5.17 (m, 2H, 2 isomers), 5.13 (s, 2H, 1 isomer), 5.12 (s, 2H, 1 isomer), 5.06 (s, 2H, 1 isomer), 5.05 (s, 2H, 1 isomer), 3.61 (t, 1H, J = 7.5 Hz, 1 isomer), 3.54 (t, 1H, J = 6.6 Hz), 2.59-2.86 (m, 3H, 2 isomers), 2.42-2.49 (m, 1H, 1 isomer), 2.24-2.31 (m, 1H, 1 isomer), 2.03-2.11 (m, 1H,2 isomers), 1.80-1.89 (m, 2H, 2 isomers), 1.22-1.35 (m, 2H, 2 isomers), 0.856 (t, 3H, J = 7.5 Hz, 1 isomer), 0.804 (t, 3H, J = 7.0 Hz, 1 isomer).

Preparation 60

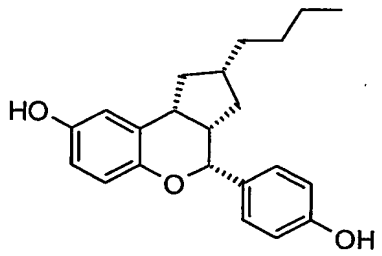
2-Benzylidene-8-benzyloxy-4-(4-benzyloxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromene



Preparation 60 can be prepared in a manner substantially similar to preparation 57 except the reaction mixture was heated to reflux overnight. Starting with preparation 50 (0.203 g, 0.427 mmol) using two addition of the Wittig reagent formed from benzyltriphenyl-phosphonium chloride affords 0.0922 g (0.167 mmol, 39 %) of a mixture of *E* and *Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.20-7.51(m, 17H, 2 isomers), 7.06 (d, 2H, J = 8.6 Hz, 2 isomers), 6.82-6.90 (m, 4H, 2 isomers), 6.26 (s, 1H, major isomer), 5.20 (s, 1H, minor isomer), 5.18 (s, 2H, minor isomer), 5.14 (s, 2H, major isomer), 5.06 (s, 2H, minor isomer), 5.03 (s, 2H, major isomer), 3.70-3.78 (m, 1H, major isomer), 3.56-3.64 (m, 1H, minor isomer), 3.12-3.25 (m, 1H, 2 isomers), 2.24-3.00 (m, 3H, 2 isomers).

Example 29

2-Butyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Dissolve preparation 59 (0.1829 g, 0.3540 mmol) in 11 mL of THF. Add a slurry of 10% Pd/C (0.0619 g) in 11 mL of isopropyl alcohol. Stir the solution under an atmosphere of hydrogen at ambient pressure and temperature overnight. Filter the solution through Celite and wash the filter cake with isopropyl alcohol and THF. Combine and concentrate the filtrate and washings and concentrate. Adsorb to 2 g of silica gel. Purify by silica gel flash chromatography eluting with 10 – 50% (1:9

MeOH/EtOAc) in hexanes to afford 0.0823 g (0.2432 mmol, 69 %) of example 31. ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.4 Hz), 6.71 (d, 1H, J = 8.4 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.77-1.90 (m, 1H), 1.40-1.46 (m, 1H), 1.14-1.26 (m, 8H), 0.863 (t, 3H, J = 6.6 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.575 min). LRMS (ES-): 337.2 (M-1).

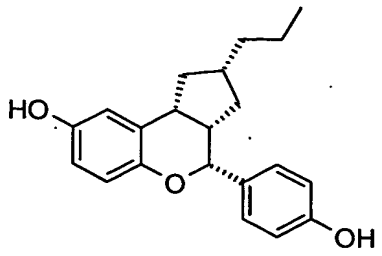
The two enantiomers can be separated by chiral preparative HPLC (Chiralpak AD, 15 % EtOH/ Heptane).

Enantiomer A: ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.4 Hz), 6.71 (d, 1H, J = 8.4 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.77-1.90 (m, 1H), 1.40-1.46 (m, 1H), 1.14-1.26 (m, 8H), 0.863 (t, 3H, J = 6.6 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.568 min). HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 3.213 min). LRMS (ES-): 337.2 (M-1).

Enantiomer B: ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.4 Hz), 6.71 (d, 1H, J = 8.4 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.77-1.90 (m, 1H), 1.40-1.46 (m, 1H), 1.14-1.26 (m, 8H), 0.863 (t, 3H, J = 6.6 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.578 min). HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 5.877 min). LRMS (ES-): 337.2 (M-1).

Example 30

4-(4-Hydroxy-phenyl)-2-propyl-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Example 32 can be prepared in a manner substantially similar to that described for example 31 starting from preparation 58 (0.1842 g, 0.3665 mmol) to afford 0.108 g (0.331 mmol, 90 %). ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.71 (d, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.80-1.92 (m, 1H), 1.38-1.46 (m, 1H), 1.14-1.30 (m, 6H), 0.849 (t, 3H, J = 7.0 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.137 min). LRMS (ES-): 323.2 (M-1).

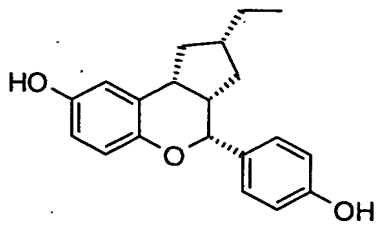
The two enantiomers can be separated by chiral preparative HPLC (Chiralpak AD, IPA/Heptane).

Enantiomer A: ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.71 (d, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.80-1.92 (m, 1H), 1.38-1.46 (m, 1H), 1.14-1.30 (m, 6H), 0.849 (t, 3H, J = 7.0 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.125 min). HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 3.477 min).
LRMS (ES-): 323.2 (M-1).

Enantiomer B: ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.71 (d, 1H, J = 8.8 Hz),6.58 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.41-3.47 (m, 1H), 2.48-2.63 (m, 2H), 1.80-1.92 (m, 1H), 1.38-1.46 (m, 1H), 1.14-1.30 (m, 6H), 0.849 (t, 3H, J = 7.0 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 11.127 min). HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 6.997 min).
LRMS (ES-): 323.2 (M-1).

Example 31

2-Ethyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Example 33 can be prepared in a manner substantially similar to that described for example 31 starting from preparation 57. ^{1}H NMR (400 MHz, MeOD): δ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J =8.4 Hz), 6.71 (d, 1H, J = 8.8 Hz), 6.59 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.42-3.48 (m, 1H), 2.49-2.63 (m, 2H), 1.71-1.83 (m, 1H), 1.40-1.47 (m, 1H), 1.15-1.26 (m, 4H), 0.829 (t, 3H, J = 7.5 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.681 min) LRMS (ES-): 309.2 (M-1).

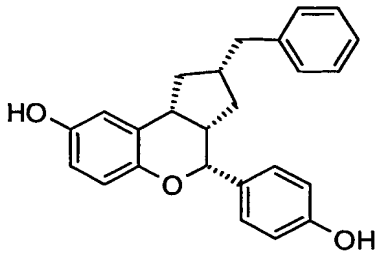
The two enantiomers can be separated by chiral preparative HPLC (Chiralpak AD, 15 % EtOH/Heptane).

Enantiomer A: ^{1}H NMR (400 MHz, MeOD): □ 7.27 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J =8.4 Hz), 6.71 (d, 1H, J = 8.8 Hz), 6.59 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.42-3.48 (m, 1H), 2.49-2.63 (m, 2H), 1.71-1.83 (m, 1H), 1.40-1.47 (m, 1H), 1.15-1.26 (m, 4H), 0.829 (t, 3H, J = 7.5 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.703 min). HPLC (Chiralpak AD, 15 % EtOH/ Heptane; 1mL/min; t_R = 3.687 min). LRMS (ES-) 309.2.

Enantiomer B: ^{1}H NMR (400 MHz, MeOD): □ 7.27 (d, 2H, J = 8.8 Hz),6.81 (d, 2H, J =8.4 Hz), 6.71 (d, 1H, J = 8.8 Hz), 6.59 (d, 1H, J = 3.1 Hz), 6.54 (dd, 1H, J = 3.1 Hz, J = 8.8 Hz), 3.42-3.48 (m, 1H), 2.49-2.63 (m, 2H), 1.71-1.83 (m, 1H), 1.40-1.47 (m, 1H), 1.15-1.26 (m, 4H), 0.829 (t, 3H, J = 7.5 Hz). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/ min; t_r 10.663 min). HPLC (Chiralpak AD, 15 % EtOH/Heptane; 1mL/min; t_R = 8.264 min). LRMS (ES-) 309.2 (M-1).

Example 32

2-Benzyl-4-(4-hydroxy-phenyl)-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]chromen-8-ol



Example 34 can be prepared in a manner substantially similar to that described for example 31 starting from preparation 60 except under an atmosphere of hydrogen at 60 psi of H_2. ^1H NMR (400 MHz, MeOD): □ 7.05 (m, 7H), 6.79 (d, 2H, J = 8.8 Hz), 6.74 (d, 1H, J = 8.4 Hz), 6.56-6.58 (m, 2H), 4.90-4.92 (m, 1H), 3.40-3.46 (m, 1H), 2.58-2.66 (m, 1H), 2.46-2.56 (m, 1H), 2.32-2.43 (m, 2H), 2.10-2.22 (m, 1H), 1.28-1.45 (m, 3H). HPLC (Zorbax C18 column; 10 to 100 % CH_3CN / H_2O for 10 min then 100 % CH_3CN for 5 min; 1 mL/min; t_r 11.269 min). LRMS(ES-): 371.2 (M-1).

Test Procedures

ER Binding Assay

The competition ER binding assay was run in a buffer containing 50 mM N-[2-hydroxyethyl]piperazine-N'–[2-ethanesulfonic acid (Hepes) pH 7.5, 1.5 mM EDTA, 150 mM NaCl, 10% glycerol, 1 mg/mL ovalbumin, 5mM DTT, 0.025 μCi per well of ^3H-Estradiol(NEN #NET517 at 118 Ci/mmol, 1 mCi/mL), and 10 ng/well ERAlpha or ERbeta Receptor (PanVera). Competing compounds were added at 10 different concentrations. Non-specific binding was determined in the presence of 1 μM of E2 (17-β Estradiol, Sigma, St. Louis, MO). The binding reaction (140 μL) was incubated for 4 hours at room temperature, then 70 μL of cold dextran coated charcoal (DCC) buffer was added to each reaction (DCC buffer was prepared by adding 0.75g of charcoal [Sigma] and 0.25g of dextran [Pharmacia] per 50 mL of assay buffer). The incubation plates were mixed for 8 minutes on an orbital shaker at 4°C and then centrifuged at 3,000 rpm for 10 minutes at 4°C. An aliquot of 120 μl of the mix was transferred to another 96-well, white flat bottom plate (Costar) and 175 μl of Wallac Optiphase Hisafe 3 scintillation fluid was

added to each well. The plates were sealed and then shaken vigorously on an orbital shaker. After an incubation of 2.5hrs, the radioactivity was counted in a Wallac Microbeta counter. The IC_{50} and percent inhibition at 10μM were calculated. The K_d for ^{3}H-Estradiol was determined by saturation binding to ERα and ERβ receptors. The IC_{50} values for compounds were converted to K_i values using the Cheng-Prusoff equation and the K_d values were determined by saturation binding assay. Compounds of Examples 1-19 and 22-25 are active in the assay as described. Preferred compounds bind to the ER beta receptor with a K_i of less than 20 nM. More preferred compounds bind to the ER beta receptor with a K_i of less than 1 nM. Compounds that are selective to binding to the ER beta receptor compared to the ER alpha receptor bind to the ER beta receptor with a lower K_i compared to the K_i for the ER alpha receptor.

As determined by the above assay, the compounds of examples 1-32 exhibit binding affinities (Kis) at the ER Alpha subtype in the range 5.0->10,000nM and to the ER beta subtype in the range of 0.20-429nM.

LNCaP Human PCa Xenograft Assay

ERbeta agonists are evaluated for their effects on the growth of androgen-sensitive LNCaP human prostatic cancer (PCa) xenografts grown in intact sexually mature (5-6 weeks old) Hsd: Athymic Nude-nu (Athymic Nude) male mice. $2.0x10^6$ LNCaP tumor cells are injected bilaterally by the subcutaneous route into the pre-tracheal region of testicular intact male mice. Mice are castrated via the scrotal route to serve as the positive control group. Test compounds are administered once per day by subcutaneous or gavage administration at multiple dose levels in a volume of 0.2 ml to xenograft-bearing mice starting on the day following tumor injection. Test compounds are reformulated weekly based on average group mean body weights. The vehicle for these studies is 1% carboxymethyl cellulose (CMC) with 0.25% Tween 80. Body weights and tumor measurements are recorded on a weekly basis and entered directly into a JMP™ (SAS; Cary, NC) spreadsheet from electronic caliper measurement. Tumor volumes in mm^3 are calculated in JMP using the following formula: L X W X H X 0.5236. Tumor and body weight responses for individual mice are recorded on a weekly basis. When LNCaP tumor volumes enter log-phase expansion, lesions are measured

every 3-4 days. Growth rates are determined using linear modeling of the log tumor values and time to treatment failure (tumor vol=1300-1500 mm^3) are determined using a linear extrapolation model (SAS; Cary, NC). Because of humane animal use considerations, animals are sacrificed when their tumor volumes approach 1200-1400 mm^3. At necropsy, final tumor measurement and body weights are recorded and whole blood is obtained via cardiac puncture and allowed to clot on ice. Serum is transferred to appropriately labeled 0.5 ml Eppendorf micro tubes, and samples are stored at -80°C for biomarker analysis.

General Rat Preparation Procedure

Seventy-five day old (unless otherwise indicated) female Sprague Dawley rats (weight range of 200 to 225g) are obtained from Charles River Laboratories (Portage, MI). The animals are either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they are housed in metal hanging cages in groups of 3 or 4 per cage and have ad libitum access to food (calcium content approximately 0.5%) and water for one week. Room temperature is maintained at $22.2^{o} \pm 1.7^{o}C$ with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

Dosing Regimen Tissue Collection: After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with a compound of formula (I) ("F-I") is initiated. 17α-ethynyl estradiol or F-I is given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or dissolved in 20% cyclodextrin. Animals are dosed daily for 4 days. Following the dosing regimen, animals are weighed and anesthetized with a ketamine: Xylazine (2:1, v:v) mixture and a blood sample is collected by cardiac puncture. The animals are then sacrificed by asphyxiation with CO_2, the uterus is removed through a midline incision, and a wet uterine weight is determined. 17α-ethynyl estradiol is obtained from Sigma Chemical Co., St. Louis, MO.

Cardiovascular Disease/Hyperlipidemia

The blood samples from above are allowed to clot at room temperature for 2 hours, and serum is obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol is determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol is oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide is then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which is read spectrophotemetrically at 500 nm. Cholesterol concentration is then calculated against a standard curve. The entire assay is automated using a Biomek Automated Workstation.

Uterine Eosinophil Peroxidase (EPO) Assay

The uteri from above are kept at 4°C until time of enzymatic analysis. The uteri are then homogenized in 50 volumes of 50 mM Tris buffer (pH 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM O-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance is monitored for one minute at 450 nm. The presence of eosinophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval is determined over the initial, linear portion of the reaction curve.

Inhibition of Bone Loss (Osteoporosis) Test Procedure

Following the general preparation procedure described above, the rats are treated daily for thirty-five days (6 rats per treatment group) and sacrificed by carbon dioxide asphyxiation on the 36th day. The thirty-five day time period is sufficient to allow maximal reduction in bone density, measured as described herein. At the time of sacrifice, the uteri are removed, dissected free of extraneous tissue, and the fluid contents are expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight is routinely reduced about 75% in response to ovariectomy. The uteri are then placed in 10% neutral buffered formalin to allow for subsequent histological analysis.

The right femurs are excised and digitilized X-rays generated and analyzed by an image analysis program (NIH image) at the distal metaphysis. The proximal aspect of the tibiae from these animals are also scanned by quantitative computed tomography. In accordance with the above procedures, F-I or ethynyl estradiol (EE_2) in 20% hydroxypropyl β-cyclodextrin are orally administered to test animals.

Therapeutic Methods of Use and Dosages

Various diseases and conditions described to be treated herein, are well known and appreciated by those skilled in the art. It is also recognized that one skilled in the art may affect the associated diseases and conditions by treating a patient presently afflicted with the diseases or conditions or by prophylactically treating a patient afflicted with the diseases or conditions with a therapeutically effective amount of the compounds of formula (I).

As used herein, the term "patient" refers to a warm blooded animal such as a mammal that is afflicted with a particular estrogen receptor-beta mediated disease. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

As used herein, the term "therapeutically effective amount" of a compound of formula (I) refers to an amount which is effective in controlling diseases and conditions associated with estrogen receptor-beta mediated diseases such as prostate cancer, benign prostatic hyperplasia, testicular cancer, cardiovascular diseases, neurodegenerative disorders, urinary incontinence, CNS disorders, GI tract disorders, and osteoporosis. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, but does include prophylactic treatment of the diseases and conditions associated with estrogen receptor-beta mediated diseases such as prostate cancer, benign prostatic hyperplasia, testicular cancer, cardiovascular diseases, neurodegenerative disorders, urinary incontinence, CNS, GI tract disorders, and osteoporosis.

A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

A therapeutically effective amount of a compound of formula (I) is expected to vary from about 0.001 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts can be determined by one skilled in the art.

In effecting treatment of a patient afflicted with the diseases and conditions described above, a compound of formula (I) can be administered in any form or mode which makes the compound bioavailable in a therapeutically effective amount, including oral, inhalation, and parenteral routes. For example, compounds of formula (I) can be administered orally, by inhalation of an aerosol or dry powder, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. Oral or inhalation administration is generally preferred for treatment of respiratory diseases, e.g. asthma. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disease or condition state to be treated, the stage of the disease or condition, and other relevant circumstances. (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their

pharmaceutically acceptable salts, such as acid addition salts or base addition salts, for purposes of stability, convenience of crystallization, increased solubility and the like.

In another embodiment, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material, which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention may be determined by someone skilled in the art.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil.

Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the compound of formula (I) present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations are able to be determined by one skilled in the art.

The compounds of the present invention may also be administered by inhalation, such as by aerosol or dry powder. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the compounds of the present invention or a formulation thereof. Formulations for administration by inhalation of compounds of formula (I) may be delivered in single phase, bi-phasic, or tri-phasic systems. A variety of systems are available for the administration by aerosols of the compounds of formula (I). Dry powder formulations are prepared by either pelletizing or milling the compound of formula (I) to a suitable particle size or by admixing the pelletized or milled compound of formula (I) with a suitable carrier material, such as lactose and the like. Delivery by inhalation includes the necessary container, activators, valves, subcontainers, and the like. Preferred aerosols and dry powder formulations for administration by inhalation are able to be determined by one skilled in the art.

The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Topical formulations may contain a concentration of the formula (I) or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.